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(54) Title: INHIBITORS OF FACTOR Xa

(57) Abstract: Novel compounds, their salts and compositions related thereto having activity against mammalian factor Xa are disclosed. The compounds are useful (*in vitro*) or (*in vivo*) for preventing or treating coagulation disorders.

INHIBITORS OF FACTOR Xa

Related Applications

This application claims benefit of priority under 35 USC § 119(e) to U.S.
5 Provisional Application No. 60/135,849 filed on May 24, 1999, which is herein
incorporated in its entirety by reference.

Field of the Invention

This invention relates to novel compounds which are potent and highly
selective inhibitors of isolated factor Xa or when assembled in the prothrombinase
10 complex. These compounds show selectivity for factor Xa versus other proteases of
the coagulation (e.g. thrombin, fVIIa, fIXa) or the fibrinolytic cascades (e.g.
plasminogen activators, plasmin). In another aspect, the present invention relates to
novel monoamidino-containing compounds, their pharmaceutically acceptable salts,
and pharmaceutically acceptable compositions thereof which are useful as potent
15 and specific inhibitors of blood coagulation in mammals. In yet another aspect, the
invention relates to methods for using these inhibitors as therapeutic agents for
disease states in mammals characterized by coagulation disorders.

Background of the Invention

Hemostasis, the control of bleeding, occurs by surgical means, or by the
20 physiological properties of vasoconstriction and coagulation. This invention is
particularly concerned with blood coagulation and ways in which it assists in
maintaining the integrity of mammalian circulation after injury, inflammation,
disease, congenital defect, dysfunction or other disruption. Although platelets and
blood coagulation are both involved in thrombus formation, certain components of
25 the coagulation cascade are primarily responsible for the amplification or
acceleration of the processes involved in platelet aggregation and fibrin deposition.

Thrombin is a key enzyme in the coagulation cascade as well as in
hemostasis. Thrombin plays a central role in thrombosis through its ability to
catalyze the conversion of fibrinogen into fibrin and through its potent platelet
30 activation activity. Direct or indirect inhibition of thrombin activity has been the
focus of a variety of recent anticoagulant strategies as reviewed by Claeson, G.,
"Synthetic Peptides and Peptidomimetics as Substrates and Inhibitors of Thrombin

and Other Proteases in the Blood Coagulation System", Blood Coag. Fibrinol. 5, 411-436 (1994). Several classes of anticoagulants currently used in the clinic directly or indirectly affect thrombin (i.e. heparins, low-molecular weight heparins, heparin-like compounds and coumarins).

- 5 A prothrombinase complex, including Factor Xa (a serine protease, the activated form of its Factor X precursor and a member of the calcium ion binding, gamma carboxyglutamyl (Gla)-containing, vitamin K dependent, blood coagulation glycoprotein family), converts the zymogen prothrombin into the active
- 10 substrates as well as at a specific receptor, factor Xa appears to have a single physiologic substrate, namely prothrombin. Since one molecule of factor Xa may be able to generate up to 138 molecules of thrombin (Elodi et al., *Thromb. Res.* 15, 617-619 (1979)), direct inhibition of factor Xa as a way of indirectly inhibiting the formation of thrombin may be an efficient anticoagulant strategy. Therefore, it has
- 15 been suggested that compounds which selectively inhibit factor Xa may be useful as *in vitro* diagnostic agents, or for therapeutic administration in certain thrombotic disorders, see e.g., WO 94/13693.

- Polypeptides derived from hematophagous organisms have been reported which are highly potent and specific inhibitors of factor Xa. United States Patent
- 20 4,588,587 describes anticoagulant activity in the saliva of the Mexican leech, *Haementeria officinalis*. A principal component of this saliva was shown to be the polypeptide factor Xa inhibitor, antistasin (ATS), by Nutt, E. *et al.*, "The Amino Acid Sequence of Antistasin, a Potent Inhibitor of Factor Xa Reveals a Repeated Internal Structure", J. Biol. Chem., 263, 10162-10167 (1988). Another potent and
- 25 highly specific inhibitor of Factor Xa, called tick anticoagulant peptide (TAP), has been isolated from the whole body extract of the soft tick *Ornithodoros moubata*, as reported by Waxman, L., *et al.*, "Tick Anticoagulant Peptide (TAP) is a Novel Inhibitor of Blood Coagulation Factor Xa" Science, 248, 593-596 (1990).

- Factor Xa inhibitory compounds which are not large polypeptide-type
- 30 inhibitors have also been reported including: Tidwell, R.R. *et al.*, "Strategies for Anticoagulation With Synthetic Protease Inhibitors. Xa Inhibitors Versus Thrombin Inhibitors", *Thromb. Res.*, 19, 339-349 (1980); Turner, A.D. *et al.*, "p-Amidino Esters as Irreversible Inhibitors of Factor IXa and Xa and Thrombin", *Biochemistry*, 25, 4929-4935 (1986); Hitomi, Y. *et al.*, "Inhibitory Effect of New Synthetic

- Protease Inhibitor (FUT-175) on the Coagulation System", *Haemostasis*, 15, 164-168 (1985); Sturzebecher, J. *et al.*, "Synthetic Inhibitors of Bovine Factor Xa and Thrombin. Comparison of Their Anticoagulant Efficiency", *Thromb. Res.*, 54, 245-252 (1989); Kam, C.M. *et al.*, "Mechanism Based Isocoumarin Inhibitors for Trypsin and Blood Coagulation Serine Proteases: New Anticoagulants", *Biochemistry*, 27, 2547-2557 (1988); Hauptmann, J. *et al.*, "Comparison of the Anticoagulant and Antithrombotic Effects of Synthetic Thrombin and Factor Xa Inhibitors", *Thromb. Haemost.*, 63, 220-223 (1990); and the like.

- Others have reported Factor Xa inhibitors which are small molecule organic compounds, such as nitrogen containing heterocyclic compounds which have amidino substituent groups, wherein two functional groups of the compounds can bind to Factor Xa at two of its active sites. For example, WO 98/28269 describes pyrazole compounds having a terminal C(=NH)-NH₂ group; WO 97/21437 describes benzimidazole compounds substituted by a basic radical which are connected to a naphthyl group via a straight or branched chain alkylene, -C(=O) or -S(=O)₂ bridging group; WO 99/10316 describes compounds having a 4-phenyl-N-alkylamidino-piperidine and 4-phenoxy-N-alkylamidino-piperidine group connected to a 3-amidinophenyl group via a carboxamidealkyleneamino bridge; and EP 798295 describes compounds having a 4-phenoxy-N-alkylamidino-piperidine group connected to an amidinonaphthyl group via a substituted or unsubstituted sulfonamide or carboxamide bridging group.

- There exists a need for effective therapeutic agents for the regulation of hemostasis, and for the prevention and treatment of thrombus formation and other pathological processes in the vasculature induced by thrombin such as restenosis and inflammation. In particular, there continues to be a need for compounds which selectively inhibit factor Xa or its precursors. Compounds that have different combinations of bridging groups and functional groups than compounds previously discovered are needed, particularly compounds which selectively or preferentially bind to Factor Xa. Compounds with a higher degree of binding to Factor Xa than to thrombin are desired, especially those compounds having good bioavailability and/or solubility.

Summary of the Invention

The present invention relates to novel compounds which inhibit factor Xa,

their pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives, and pharmaceutically acceptable compositions thereof which have particular biological properties and are useful as potent and specific inhibitors of blood coagulation in mammals. In another aspect, the invention relates to methods of using these inhibitors as diagnostic reagents or as therapeutic agents for disease states in mammals which have coagulation disorders, such as in the treatment or prevention of any thrombotically mediated acute coronary or cerebrovascular syndrome, any thrombotic syndrome occurring in the venous system, any coagulopathy, and any thrombotic complications associated with extracorporeal circulation or instrumentation, and for the inhibition of coagulation in biological samples.

In certain embodiments, this invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation cascade (e.g. thrombin, etc.) or the fibrinolytic cascade, and are useful as diagnostic reagents as well as antithrombotic agents.

In a preferred embodiment, the present invention provides a compound of the formula I:

A-Y-D-E-G-J-Z-L

wherein:

A is selected from:

- (a) C₁-C₆-alkyl;
- (b) C₃-C₈-cycloalkyl;
- (c) phenyl, which is independently substituted with 0-2 R¹ substituents;
- (d) naphthyl, which is independently substituted with 0-2 R¹ substituents; and
- (e) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R¹ substituents;

R¹ is selected from:

Halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, -NO₂, (CH₂)_mNR²R³, SO₂NR²R³, SO₂R², CF₃, OR², and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, -CN C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl and -NO₂;

R² and R³ are independently selected from the group consisting of:

H, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, C₀₋₄alkylphenyl and C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂;

m is an integer of 0-2;

Y is a member selected from the group consisting of:

a direct link, -C(=O)-, -N(R⁴)-, -C(=O)-N(R⁴)-, -N(R⁴)-C(=O)-, -SO₂-, -O-, -SO₂-N(R⁴)- and -N(R⁴)-SO₂-;

R⁴ is selected from:

H, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, C₀₋₄alkylphenyl and C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂;

D is a direct link or is a member selected from the group consisting of:

- (a) phenyl, which is independently substituted with 0-2 R^{1a} substituents;
- (b) naphthyl, which is independently substituted with 0-2 R^{1a} substituents; and

- (c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1a} substituents;

5 R^{1a} is selected from:

Halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, -NO₂, (CH₂)_mNR^{2a}R^{3a}, SO₂NR^{2a}R^{3a}, SO₂R^{2a}, CF₃, OR^{2a}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, C₀₋₄alkylphenyl and C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

20 E is a member selected from the group consisting of:

-N(R⁵)-C(=O)-, -N(R⁵)-C(=O)-CH₂-, -C(=O)-N(R⁵)-, -C(=O)-N(R⁵)-CH₂-,
-N(R⁵)-C(=O)-N(R⁶)-, -SO₂-N(R⁵)-, -N(R⁵)-SO₂-N(R⁶)- and -N(R⁵)-SO₂-N(R⁶)-C(=O)-;

R⁵ and R⁶ are independently selected from:

25 H, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, C₀₋₄alkylphenyl, C₀₋₄alkylnaphthyl, C₀₋₄alkylheteroaryl, C₁₋₄alkylCOOH and C₁₋₄alkylCOOC₁₋₄alkyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl, naphthyl and heteroaryl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

G is selected from:



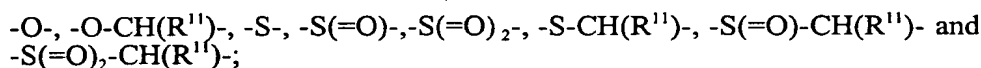
wherein R^7 , R^8 , R^{7a} , R^{8a} , R^{7b} and R^{8b} are independently a member selected from the group consisting of:

- 5 hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{0-4} alkyl- C_{3-8} cycloalkyl, C_{0-4} alkylphenyl, C_{0-4} alkylnaphthyl, C_{0-4} alkylimidazolyl, $-\text{OR}^9$, $-\text{C}_{0-4}$ alkylCOOR⁹, $-\text{C}_{0-4}$ alkylC(=O)NR⁹R¹⁰, $-\text{C}_{0-4}$ alkylC(=O)NR⁹-CH₂-CH₂-O-R¹⁰, $-\text{C}_{0-4}$ alkylC(=O)NR⁹(-CH₂-CH₂-O-R¹⁰)-, $-\text{N}(\text{R}^9)\text{COR}^{10}$, $-\text{N}(\text{R}^9)\text{C(=O)R}^{10}$, $-\text{N}(\text{R}^9)\text{SO}_2\text{R}^{10}$, and a naturally occurring or synthetic amino acid side chain, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{0-4} alkyl- C_{3-8} cycloalkyl, $-\text{CN}$, $-\text{OH}$, $-\text{OC}_{1-4}$ alkyl, $-\text{OC}_{1-4}$ alkyl-OMe, $-\text{OCH}_2\text{COOH}$, and $-\text{NO}_2$;

- 15 R^9 and R^{10} are independently selected from:

- H, C_{1-4} alkyl, C_{0-8} cycloalkyl, C_{0-4} alkylphenyl and C_{0-4} alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{0-4} alkyl- C_{3-8} cycloalkyl, $-\text{CN}$ and $-\text{NO}_2$, and wherein R^9 and R^{10} taken together can form a 5-8 membered heterocyclic ring;

J is a member selected from the group consisting of:



- 25 R^{11} is a member selected from the group consisting of:

- hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{0-4} alkyl- C_{3-8} cycloalkyl, C_{0-4} alkylphenyl, C_{0-4} alkylnaphthyl, C_{0-4} alkylheterocyclic ring having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S, $\text{CH}_2\text{COOC}_{1-4}$ alkyl, $\text{CH}_2\text{COOC}_{1-4}$ alkylphenyl and $\text{CH}_2\text{COOC}_{1-4}$ alkylnaphthyl;

Z is a member selected from the group consisting of:

- (a) phenyl, which is independently substituted with 0-2 R^{1b} substituents;
- (b) naphthyl, which is independently substituted with 0-2 R^{1b} substituents; and
- (c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1b} substituents;

R^{1b} is selected from:

- Halo, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{0-4} alkyl C_{3-8} cycloalkyl, -CN, -NO₂, $NR^{2b}R^{3b}$, $SO_2NR^{2b}R^{3b}$, SO_2R^{2b} , CF_3 , OR^{2b} , $O-CH_2-OPh$, $O-CH_2-Ph$, $O-CH_2-CH_2-OR^{2b}$, $O-CH_2-COOR^{2b}$, $N(R^{2b})-CH_2-CH_2-OR^{2b}$, $N(-CH_2-CH_2-OR^{2b})_2$, $N(R^{2b})-C(=O)R^{3b}$, $N(R^{2b})-SO_2-R^{3b}$, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{0-4} alkyl C_{3-8} cycloalkyl, -CN and -NO₂;

R^{2b} and R^{3b} are independently selected from the group consisting of:

- H, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{0-4} alkyl C_{3-8} cycloalkyl, C_{0-4} alkylphenyl and C_{0-4} alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{0-4} alkyl C_{3-8} cycloalkyl, -CN and -NO₂;

L is selected from:

H, -CN, $C(=O)NR^{12}R^{13}$, $(CH_2)_nNR^{12}R^{13}$, $C(=NR^{12})NR^{12}R^{13}$, $NR^{12}R^{13}$, OR^{12} , $-NR^{12}C(=NR^{12})NR^{12}R^{13}$, and $NR^{12}C(=NR^{12})-R^{13}$;

R^{12} and R^{13} are independently selected from:

- hydrogen, $-OR^{14}$, $-NR^{14}R^{15}$, C_{1-4} alkyl, C_{0-4} alkylphenyl, C_{0-4} alkylnaphthyl, $COOC_{1-4}$ alkyl, $COO-C_{0-4}$ alkylphenyl and $COO-C_{0-4}$ alkylnaphthyl, wherein

from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂;

5 R¹⁴ and R¹⁵ are independently selected from:

10 H, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, C₀₋₄alkylphenyl and C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

15 In certain aspects of this invention, compounds are provided which are useful as diagnostic reagents. In another aspect, the present invention includes pharmaceutical compositions comprising a pharmaceutically effective amount of the compounds of this invention and a pharmaceutically acceptable carrier. In yet another aspect, the present invention includes methods comprising using the above compounds and pharmaceutical compositions for preventing or treating disease
20 states characterized by undesired thrombosis or disorders of the blood coagulation process in mammals, or for preventing coagulation in biological samples such as, for example, stored blood products and samples. Optionally, the methods of this invention comprise administering the pharmaceutical composition in combination with an additional therapeutic agent such as an antithrombotic and/or a thrombolytic
25 agent and/or an anticoagulant.

The preferred compounds also include their pharmaceutically acceptable isomers, hydrates, solvates, salts and prodrug derivatives.

Detailed Description of the Invention

30 Definitions

In accordance with the present invention and as used herein, the following

terms are defined with the following meanings, unless explicitly stated otherwise.

The term "alkenyl" refers to a trivalent straight chain or branched chain unsaturated aliphatic radical. The term "alkinyl" (or "alkynyl") refers to a straight or branched chain aliphatic radical that includes at least two carbons joined by a triple bond. If no number of carbons is specified alkenyl and alkynyl each refer to radicals having from 2-12 carbon atoms.

The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched-chain and cyclic groups having the number of carbon atoms specified, or if no number is specified, having up to 12 carbon atoms. The term "cycloalkyl" as used herein refers to a mono-, bi-, or tricyclic aliphatic ring having 3 to 14 carbon atoms and preferably 3 to 7 carbon atoms.

As used herein, the terms "carbocyclic ring structure" and "C₃₋₁₆ carbocyclic mono, bicyclic or tricyclic ring structure" or the like are each intended to mean stable ring structures having only carbon atoms as ring atoms wherein the ring structure is a substituted or unsubstituted member selected from the group consisting of: a stable monocyclic ring which is aromatic ring ("aryl") having six ring atoms; a stable monocyclic non-aromatic ring having from 3 to 7 ring atoms in the ring; a stable bicyclic ring structure having a total of from 7 to 12 ring atoms in the two rings wherein the bicyclic ring structure is selected from the group consisting of ring structures in which both of the rings are aromatic, ring structures in which one of the rings is aromatic and ring structures in which both of the rings are non-aromatic; and a stable tricyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein the tricyclic ring structure is selected from the group consisting of: ring structures in which three of the rings are aromatic, ring structures in which two of the rings are aromatic and ring structures in which three of the rings are non-aromatic. In each case, the non-aromatic rings when present in the monocyclic, bicyclic or tricyclic ring structure may independently be saturated, partially saturated or fully saturated. Examples of such carbocyclic ring structures include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), 2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin). Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any carbon atom which results in a stable structure. The term "substituted" as used in conjunction with carbocyclic

ring structures means that hydrogen atoms attached to the ring carbon atoms of ring structures described herein may be substituted by one or more of the substituents indicated for that structure if such substitution(s) would result in a stable compound.

The term "aryl" which is included with the term "carbocyclic ring structure" refers to an unsubstituted or substituted aromatic ring, substituted with one, two or three substituents selected from loweralkoxy, loweralkyl, loweralkylamino, hydroxy, halogen, cyano, hydroxyl, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxyl, carboalkoxy and carboxamide, including but not limited to carbocyclic aryl, heterocyclic aryl, and biaryl groups and the like, all of which may be optionally substituted. Preferred aryl groups include phenyl, halophenyl, loweralkylphenyl, naphthyl, biphenyl, phenanthrenyl and naphthacenyl.

The term "arylalkyl" which is included with the term "carbocyclic aryl" refers to one, two, or three aryl groups having the number of carbon atoms designated, appended to an alkyl group having the number of carbon atoms designated. Suitable arylalkyl groups include, but are not limited to, benzyl, picolyl, naphthylmethyl, phenethyl, benzyhydrl, trityl, and the like, all of which may be optionally substituted.

As used herein, the term "heterocyclic ring" or "heterocyclic ring system" is intended to mean a substituted or unsubstituted member selected from the group consisting of stable monocyclic ring having from 5-7 members in the ring itself and having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S; a stable bicyclic ring structure having a total of from 7 to 12 atoms in the two rings wherein at least one of the two rings has from 1 to 4 hetero atoms selected from N, O and S, including bicyclic ring structures wherein any of the described stable monocyclic heterocyclic rings is fused to a hexane or benzene ring; and a stable tricyclic heterocyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein at least one of the three rings has from 1 to 4 hetero atoms selected from the group consisting of N, O and S. Any nitrogen and sulfur atoms present in a heterocyclic ring of such a heterocyclic ring structure may be oxidized. Unless indicated otherwise the terms "heterocyclic ring" or "heterocyclic ring system" include aromatic rings, as well as non-aromatic rings which can be saturated, partially saturated or fully saturated non-aromatic rings. Also, unless indicated otherwise the term "heterocyclic ring system" includes ring structures wherein all of the rings contain at least one hetero atom as well as structures having

less than all of the rings in the ring structure containing at least one hetero atom, for example bicyclic ring structures wherein one ring is a benzene ring and one of the rings has one or more hetero atoms are included within the term "heterocyclic ring systems" as well as bicyclic ring structures wherein each of the two rings has at least one hetero atom. Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any hetero atom or carbon atom which results in a stable structure. Further, the term "substituted" means that one or more of the hydrogen atoms on the ring carbon atom(s) or nitrogen atom(s) of the each of the rings in the ring structures described herein may be replaced by one or more of the indicated substituents if such replacement(s) would result in a stable compound. Nitrogen atoms in a ring structure may be quaternized, but such compounds are specifically indicated or are included within the term "a pharmaceutically acceptable salt" for a particular compound. When the total number of O and S atoms in a single heterocyclic ring is greater than 1, it is preferred that such atoms not be adjacent to one another. Preferably, there are no more than 1 O or S ring atoms in the same ring of a given heterocyclic ring structure.

Examples of monocyclic and bicyclic heterocyclic ring systems, in alphabetical order, are acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolyl, 1H-indazolyl, indolinyl, indoliziny, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinoliziny, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl,

thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl. Preferred heterocyclic ring structures include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, 5 benzimidazolyl, 1H-indazolyl, oxazolinyl, or isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocyclic ring structures.

As used herein the term "aromatic heterocyclic ring system" has essentially the same definition as for the monocyclic and bicyclic ring systems except that at least one ring of the ring system is an aromatic heterocyclic ring or the bicyclic ring 10 has an aromatic or non-aromatic heterocyclic ring fused to an aromatic carbocyclic ring structure.

The terms "halo" or "halogen" as used herein refer to Cl, Br, F or I substituents. The term "haloalkyl", and the like, refer to an aliphatic carbon radicals having at least one hydrogen atom replaced by a Cl, Br, F or I atom, including 15 mixtures of different halo atoms. Trihaloalkyl includes trifluoromethyl and the like as preferred radicals, for example.

The term "methylene" refers to $-CH_2-$.

The term "pharmaceutically acceptable salts" includes salts of compounds derived from the combination of a compound and an organic or inorganic acid. 20 These compounds are useful in both free base and salt form. In practice, the use of the salt form amounts to use of the base form; both acid and base addition salts are within the scope of the present invention.

"Pharmaceutically acceptable acid addition salt" refers to salts retaining the biological effectiveness and properties of the free bases and which are not 25 biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, 30 ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

"Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium,

magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases include salts of primary, secondary, and tertiary amines, substituted amines
5 including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine,
10 purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline, and caffeine.

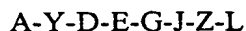
"Biological property" for the purposes herein means an *in vivo* effector or antigenic function or activity that is directly or indirectly performed by a compound
15 of this invention that are often shown by *in vitro* assays. Effector functions include receptor or ligand binding, any enzyme activity or enzyme modulatory activity, any carrier binding activity, any hormonal activity, any activity in promoting or inhibiting adhesion of cells to an extracellular matrix or cell surface molecules, or any structural role. Antigenic functions include possession of an epitope or
20 antigenic site that is capable of reacting with antibodies raised against it.

In the compounds of this invention, carbon atoms bonded to four non-identical substituents are asymmetric. Accordingly, the compounds may exist as diastereoisomers, enantiomers or mixtures thereof. The syntheses described herein may employ racemates, enantiomers or diastereomers as starting materials or
25 intermediates. Diastereomeric products resulting from such syntheses may be separated by chromatographic or crystallization methods, or by other methods known in the art. Likewise, enantiomeric product mixtures may be separated using the same techniques or by other methods known in the art. Each of the asymmetric carbon atoms, when present in the compounds of this invention, may be in one of
30 two configurations (R or S) and both are within the scope of the present invention.

Preferred Embodiments

In a preferred embodiment, the present invention provides a compound

according to the formula I:



wherein:

A is selected from:

- 5 (a) $\text{C}_1\text{-C}_6\text{-alkyl}$;
- (b) $\text{C}_3\text{-C}_8\text{-cycloalkyl}$;
- (c) phenyl, which is independently substituted with 0-2 R^1 substituents;
- (d) naphthyl, which is independently substituted with 0-2 R^1 substituents;
- and
- 10 (e) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^1 substituents;

R^1 is selected from:

- 15 halo, $\text{C}_{1-4}\text{alkyl}$, $-\text{CN}$, $(\text{CH}_2)_m\text{NR}^2\text{R}^3$, $\text{SO}_2\text{NR}^2\text{R}^3$, SO_2R^2 , CF_3 , OR^2 , and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S;

R^2 and R^3 are independently selected from the group consisting of:

H, $\text{C}_{1-4}\text{alkyl}$ and $\text{C}_{0-4}\text{alkylaryl}$,

- 20 m is an integer of 0-2;

Y is a member selected from the group consisting of:

a direct link, $-\text{C}(=\text{O})-$, $-\text{N}(\text{R}^4)-$, $-\text{C}(=\text{O})-\text{N}(\text{R}^4)-$, $-\text{N}(\text{R}^4)-\text{C}(=\text{O})-$, $-\text{SO}_2-$, $-\text{O}-$, $-\text{SO}_2-\text{N}(\text{R}^4)-$ and $-\text{N}(\text{R}^4)-\text{SO}_2-$;

R^4 is selected from:

- 25 H, $\text{C}_{1-4}\text{alkyl}$ and $\text{C}_{0-4}\text{alkylaryl}$;

D is absent or is a member selected from the group consisting of:

- (a) aryl, which is independently substituted with 0-2 R^{1a} substituents; and

- (b) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1a} substituents;

5 R^{1a} is selected from:

Halo, C_{1-4} alkyl, -CN, -NO₂, $(CH_2)_mNR^{2a}R^{3a}$, $SO_2NR^{2a}R^{3a}$, SO_2R^{2a} , CF₃, OR^{2a}, and a 5-6 membered aromatic heterocyclic ring containing from 1-4 heteroatoms selected from N, O and S;

R^{2a} and R^{3a} are independently selected from the group consisting of:

10 H, C_{1-4} alkyl and C_{0-4} alkylaryl;

E is a member selected from the group consisting of:

-N(R⁵)-C(=O)-, -N(R⁵)-C(=O)-CH₂-, -C(=O)-N(R⁵)-, -C(=O)-N(R⁵)-CH₂-,
-N(R⁵)-C(=O)-N(R⁶)-, -SO₂-N(R⁵)-, -N(R⁵)-SO₂-N(R⁶)- and -N(R⁵)-SO₂-N(R⁶)-C(=O)-;

15 R^5 and R^6 are independently selected from:

H, C_{1-4} alkyl, C_{0-4} alkylaryl, C_{0-4} alkylheteroaryl, C_{1-4} alkylCOOH and C_{1-4} alkylCOOC₁₋₄alkyl;

G is selected from:

-CR⁷R⁸- and -CR^{7a}R^{8a}-CR^{7b}R^{8b}-

20 wherein R^7 , R^8 , R^{7a} , R^{8a} , R^{7b} and R^{8b} are independently a member selected from from the group consisting of:

hydrogen, C_{1-4} alkyl, C_{0-4} alkyl- C_{3-8} cycloalkyl, C_{0-4} alkylaryl,
-OR⁹-, C_{0-4} alkylCOOR⁹-, C_{0-4} alkylC(=O)NR⁹R¹⁰-, -N(R⁹)COR¹⁰-,
N(R⁹)C(=O)R¹⁰-, -N(R⁹)SO₂R¹⁰-, and common amino acid side chains;

25 R^9 and R^{10} are independently selected from:

H, C_{1-4} alkyl and C_{0-4} alkylaryl;

J is a member selected from the group consisting of:

-O-, -O-CH(R¹¹)-, -S- and -S-CH(R¹¹)-;

R¹¹ is a member selected from the group consisting of:

hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylaryl, C₀₋₄alkylheterocyclics, CH₂COOC₁₋₄alkyl, CH₂COOC₁₋₄alkylaryl;

5 Z is a member selected from the group consisting of:

- (a) aryl, which is independently substituted with 0-2 R^{1b} substituents; and
- (b) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1b} substituents;

10

R^{1b} is selected from:

halo, C₁₋₄alkyl, -CN, -NO₂, NR^{2b}R^{3b}, SO₂NR^{2b}R^{3b}, SO₂R^{2b}, CF₃, OR^{2b}, O-CH₂-CH₂-OR^{2b}, O-CH₂-COOR^{2b}, N(R^{2b})-CH₂-CH₂-OR^{2b}, N(-CH₂-CH₂-OR^{2b})₂, N(R^{2b})-C(=O)R^{3b}, N(R^{2b})-SO₂-R^{3b}, and a 5-6 membered aromatic heterocyclic ring containing from 1-4 heteroatoms selected from N, O and S;

15

R^{2b} and R^{3b} are independently selected from the group consisting of:

H, C₁₋₄alkyl and C₀₋₄alkylaryl;

L is selected from:

H, -CN, C(=O)NR¹²R¹³, (CH₂)_nNR¹²R¹³, C(=NR¹²)NR¹²R¹³, NR¹²R¹³, OR¹², -NR¹²C(=NR¹²)NR¹²R¹³ and NR¹²C(=NR¹²)-R¹³;

20

R¹² and R¹³ are independently selected from:

hydrogen, -OR¹⁴, -NR¹⁴R¹⁵, C₁₋₄alkyl, C₀₋₄alkylaryl, COOC₁₋₄alkyl, and COO-C₀₋₄alkylaryl;

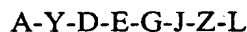
R¹⁴ and R¹⁵ are independently selected from:

25

H and C₁₋₄alkyl; and

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In a further preferred embodiment, the present invention provides a compound according to the formula I:



wherein:

5 A is selected from:

- (a) phenyl, which is independently substituted with 0-2 R^1 substituents; and
- (b) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^1 substituents;

R^1 is selected from:

halo, $(\text{CH}_2)_m\text{NR}^2\text{R}^3$, $\text{SO}_2\text{NR}^2\text{R}^3$ and SO_2R^2 ;

R^2 and R^3 are independently selected from the group consisting of:

15 H and C_{1-4} alkyl;

Y is a member selected from the group consisting of:

a direct link, $-\text{C}(=\text{O})-$, $-\text{SO}_2-$ and $-\text{O}-$;

D is a member selected from the group consisting of:

- (a) phenyl, which is independently substituted with 0-2 R^{1a} substituents; and
- (b) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1a} substituents;

25 R^{1a} is selected from:

Halo and C_{1-4} alkyl;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, C₁₋₄alkyl, C₀₋₄alkylaryl;

E is a member selected from the group consisting of:

-N(R⁵)-C(=O)- and -C(=O)-N(R⁵)-;

R⁵ and R⁶ are independently selected from:

5 H, C₁₋₄alkyl, C₀₋₄alkylaryl and C₀₋₄alkylheteroaryl;

G is selected from:

-CR⁷R⁸- and -CR^{7a}R^{8a}-CR^{7b}R^{8b}-

wherein R⁷, R⁸, R^{7a}, R^{8a}, R^{7b} and R^{8b} are independently a member selected from from the group consisting of:

10 hydrogen, C₁₋₄alkyl, C₀₋₄alkyl-C₃₋₈cycloalkyl, C₀₋₄alkylaryl, -C₀₋₄alkylCOOR⁹, -OR⁹, -C₀₋₄alkylC(=O) NR⁹R¹⁰, -C₀₋₄alkylC(=O)NR⁹-CH₂-CH₂-O-R¹⁰, -C₀₋₄alkylC(=O)NR⁹(-CH₂-CH₂-O-R¹⁰)₂, -N(R⁹)COR¹⁰, -N(R⁹)C(=O)R¹⁰, -N(R⁹)SO₂R¹⁰, and common amino acid side chains;

R⁹ and R¹⁰ are independently selected from:

15 H and C₁₋₄alkyl, wherein the NR⁹R¹⁰ group of R⁷, R⁸, R^{7a}, R^{8a}, R^{7b} and R^{8b} is optionally cyclized to form a 5-8 membered heterocyclic group;

J is a member selected from the group consisting of:

-O-, -O-CH(R¹¹)-, -S- and -S-CH(R¹¹)-;

R¹¹ is a member selected from the group consisting of:

20 hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, C₀₋₄alkylaryl and a C₀₋₄alkylheterocyclic ring;

Z is a member selected from the group consisting of:

- (a) phenyl, which is independently substituted with 0-2 R^{1b} substituents;
- (b) an aromatic heterocyclic ring having from 5 to 10 ring atoms, wherein 1-4 ring atoms are selected from N, O and S, and wherein the ring may be substituted independently by from 0-2 R^{1b} substituents; and
- 25

- (c) a fused aromatic bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, wherein the bicyclic ring system may be substituted with 0-2 R^{1b} substituents;

5 R^{1b} is selected from:

halo, C_{1-4} alkyl, OH, OBn, $O-CH_2-CH_2-OH$, $O-CH_2-CH_2-OCH_3$, $O-CH_2-COOH$, $O-CH_2-C(=O)-O-CH_3$, NH_2 , $NH-CH_2-CH_2-O-CH_3$, $NH-C(=O)-O-CH_3$, and $NH-SO_2-CH_3$;

L is selected from:

10 H, $C(=O)NR^{12}R^{13}$, $(CH_2)_nNR^{12}R^{13}$ and $C(=NR^{12})NR^{12}R^{13}$;

R^{12} and R^{13} are independently selected from:

hydrogen and C_{1-4} alkyl;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

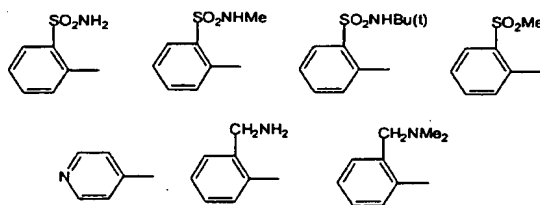
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In a further preferred embodiment, the present invention provides a compound according to formula I:

A-Y-D-E-G-J-Z-L

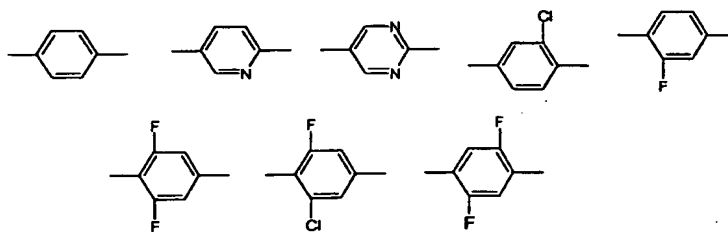
wherein

20 A is a member selected from the group consisting of:



Y is a direct link;

D is a member selected from the group consisting of:



5 E is a member selected from the group consisting of:

-C(=O)-NH-, -C(=O)-N(-CH₃)-, C(=O)-N(-Bn)-, -NH-C(=O)-, -N(-CH₃)-C(=O)- and -N(-Bn)C(=O)-;

G is selected from:

10 -CH-(-NH₂)-CH₂-, -CH-(-NH(C(=O)-CH₃))-CH₂-,
-CH-(-NH(C(=O)-Ph))-CH₂-, -CH-(C(=O)-OR⁸)-, -CH(-R⁷)-,
-CH₂-CH(C(=O)-OR⁸)-, and -CH₂-CH(C(=O)-N(-R⁸, -R⁸))-;

R⁷ is a member selected from the group consisting of :

H, phenyl, Bn, -O-loweralkyl, and cyclohexyl;

R⁸ is a member selected from the group consisting of:

15 H, C₁₋₆alkyl, - O-loweralkyl and C₃₋₆cycloalkyl;

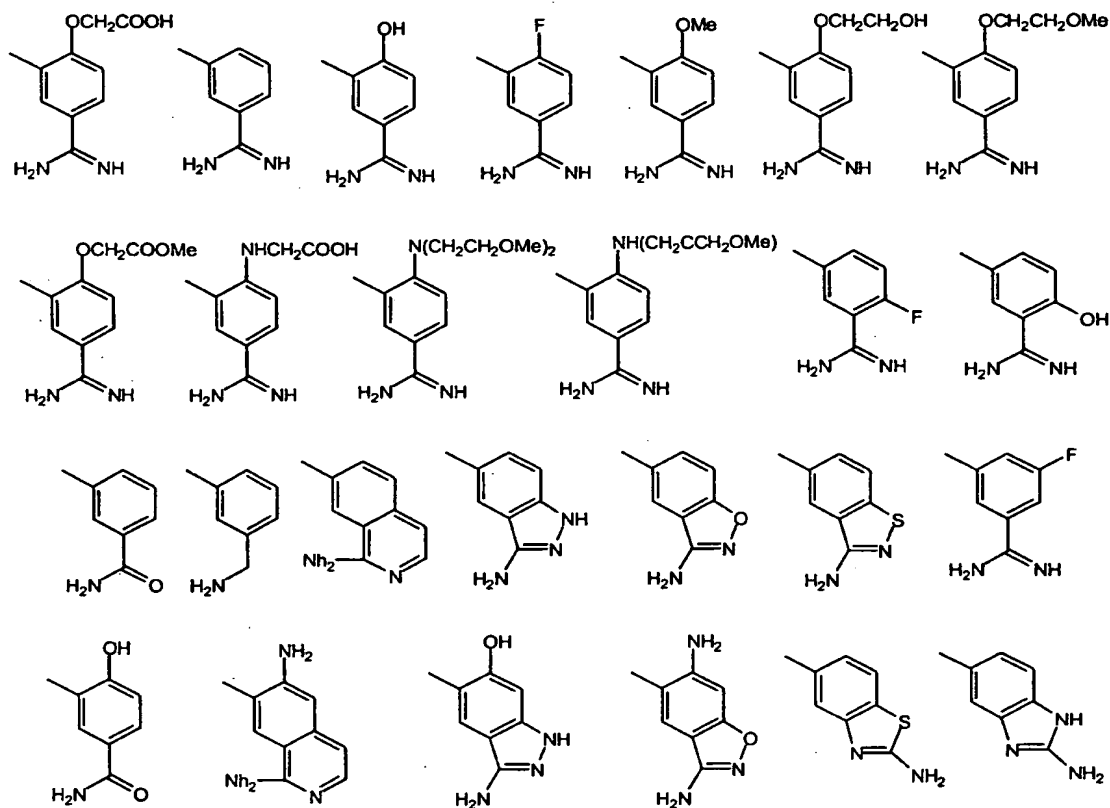
J is a member selected from the group consisting of;

-O-, -O-CH(R¹¹)-, -S- and -S- CH(R¹¹)-;

R¹¹ is a member selected from the group consisting of:

H, methyl, phenyl and benzyl; and

Z and L taken together are a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and

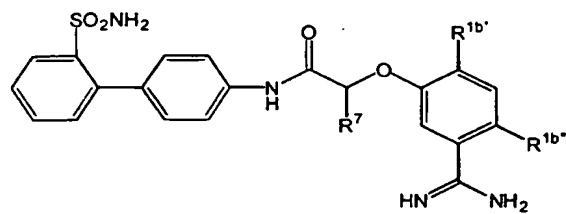
5 prodrug derivatives thereof.

The following non-limiting tables illustrate representative compounds of the present invention:

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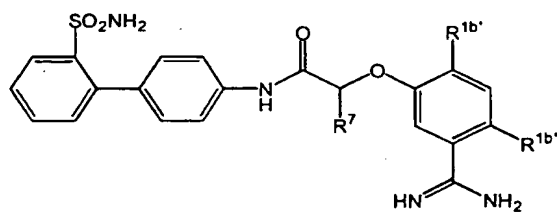
Table 1



Formula II

R ⁷	R ^{1b'}	R ^{1b''}
H	H	H
Me	H	OH
	F	H
	-OH	F
	Br	OH
	-NH ₂	OH
	OCH ₂ Ph	F
	OCH ₂ CH ₂ OMe	H
	H	H
	H	H

Table 1a



Formula II




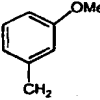
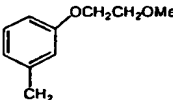
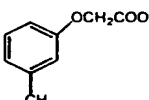


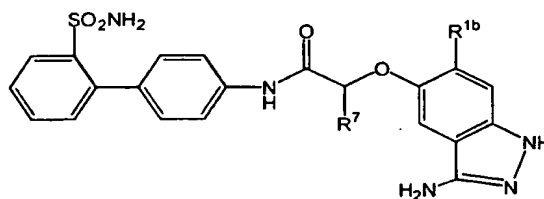
R ⁷	R ^{1b'}	R ^{1b''}
H	H	H
Me	H	OH
	F	H
	-OH	F
	Br	OH
	-NH ₂	OH
	OCH ₂ Ph	F
	OCH ₂ CH ₂ OMe	H
	H	H
	H	H

Table 2



Formula III


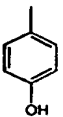


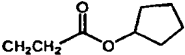
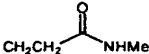
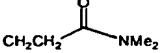
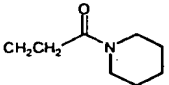
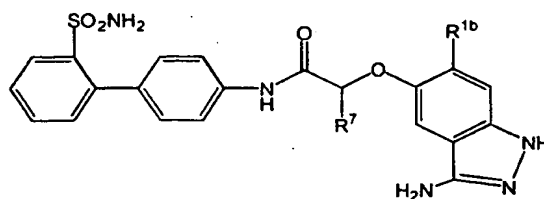
R ⁷	R ^{1b}
H	H
Me	H
	F
	-OH
	Br
	-NH ₂
	OCH ₂ Ph
	OCH ₂ CH ₂ OMe
	H
	H

Table 2a



Formula III



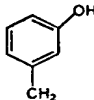

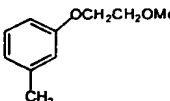
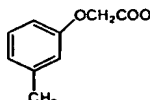


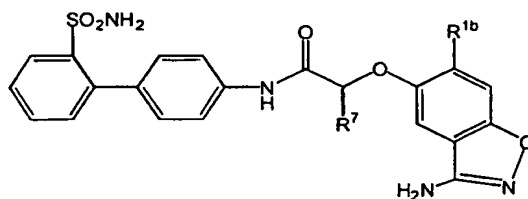
R ⁷	R ^{1b}
H	H
Me	H
	F
	-OH
	Br
	-NH ₂
	OCH ₂ Ph
	OCH ₂ CH ₂ OMe
	H
	H

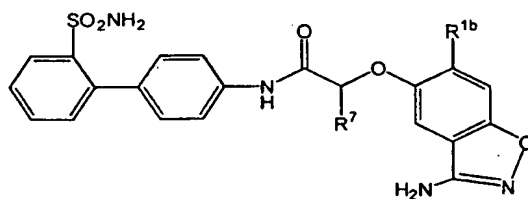
Table 3



Formula IV

R ⁷	R ^{1b}
H	H
Me	H
	F
	-OH
	Br
	-NH ₂
	OCH ₂ Ph
	OCH ₂ CH ₂ OMe
	H
	H

Table 3a



Formula IV



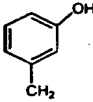
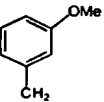
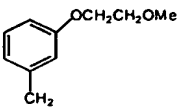
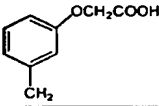


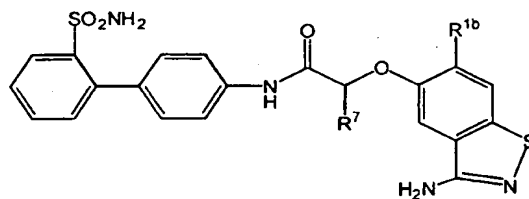
R ⁷	R ^{1b}
H	H
Me	H
	F
	-OH
	Br
	-NH ₂
	OCH ₂ Ph
	OCH ₂ CH ₂ OMe
	H
	H

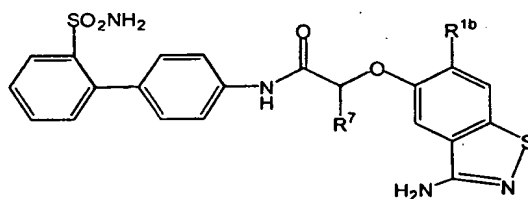
Table 4



Formula V.

R ⁷	R ^{1b}
H	H
Me	H
	F
	-OH
	Br
	-NH ₂
	OCH ₂ Ph
	OCH ₂ CH ₂ OMe
	H
	H

Table 4a



Formula V



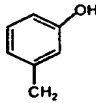
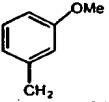
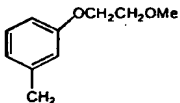
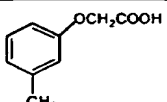


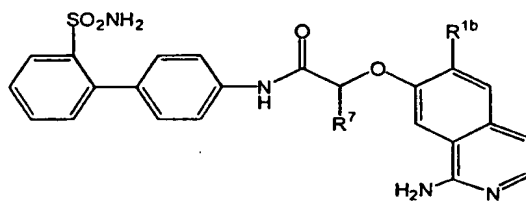
R ⁷	R ^{1b}
H	H
Me	H
	F
	-OH
	Br
	-NH ₂
	OCH ₂ Ph
	OCH ₂ CH ₂ OMe
	H
	H

Table 5



Formula VI


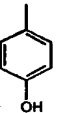


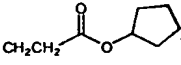
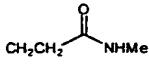
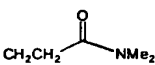
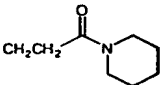
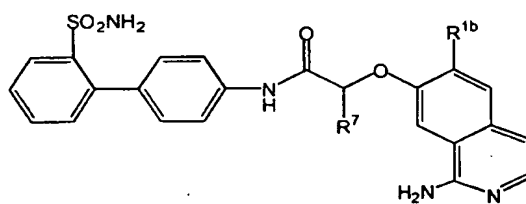
R^7	R^{1b}
H	H
Me	H
	F
	-OH
	Br
	-NH ₂
	OCH ₂ Ph
	OCH ₂ CH ₂ OMe
	H
	H

Table 5a



Formula VI


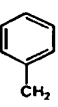
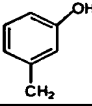
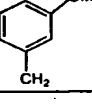
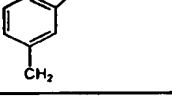
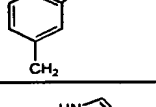
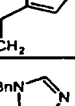
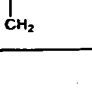
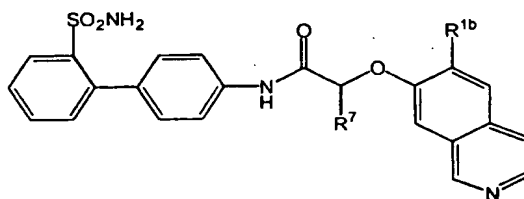
R ⁷	R ^{1b}
H	H
Me	H
	F
	-OH
	Br
	-NH ₂
	OCH ₂ Ph
	OCH ₂ CH ₂ OMe
	H
	H

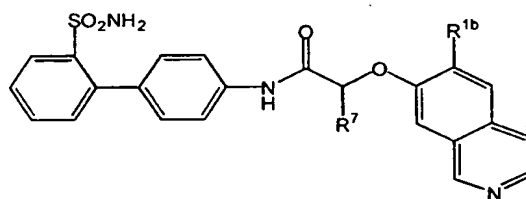
Table 6



Formula VII

R ⁷	R ^{1b}
H	H
Me	H
	F
	-OH
	Br
	-NH ₂
	OCH ₂ Ph
	OCH ₂ CH ₂ OMe
	H
	H

Table 6a



Formula VII



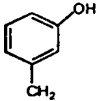
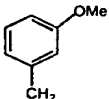
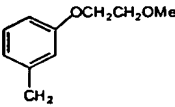
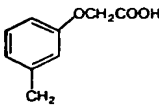


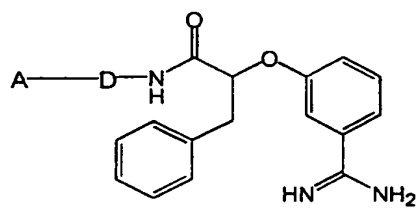
R^7	R^{1b}
H	H
Me	H
	F
	-OH
	Br
	-NH ₂
	OCH ₂ Ph
	OCH ₂ CH ₂ OMe
	H
	H

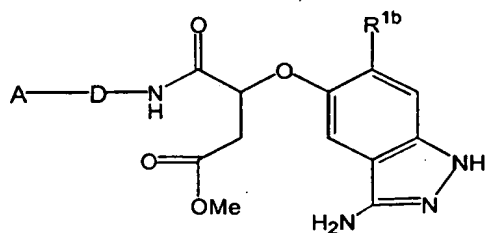
Table 7



Formula VIII

A	D	A	D

Table 8



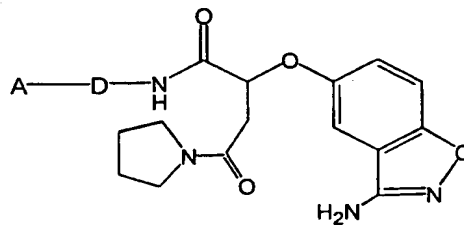
Formula IX

A	D	A	D

wherein R^{1b} is a member selected from the group consisting of H, F, -OH,

Br, Cl, -NH₂, -O-CH₂-O-Ph and -O-CH₂-CH₂-O-CH₃,

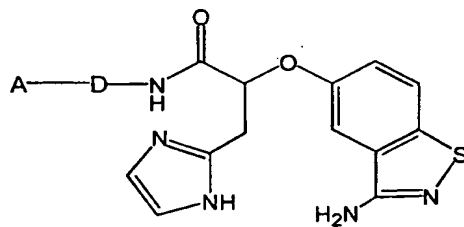
Table 9



Formula X

A	D	A	D

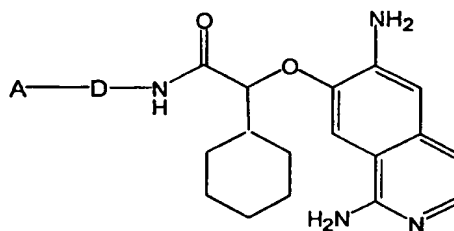
Table 10



Formula XI

A	D	A	D

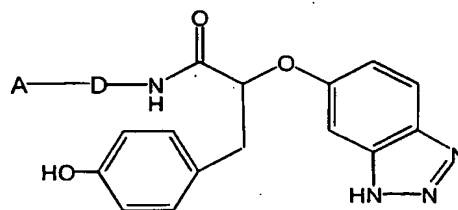
Table 11



Formula XII

A	D	A	D

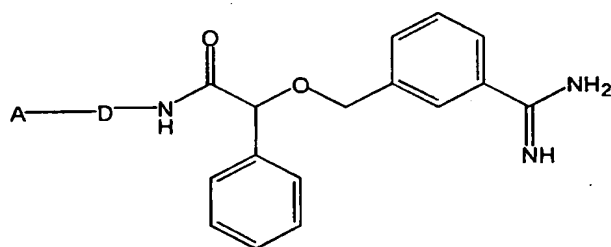
Table 12



Formula XIII

A	D	A	D

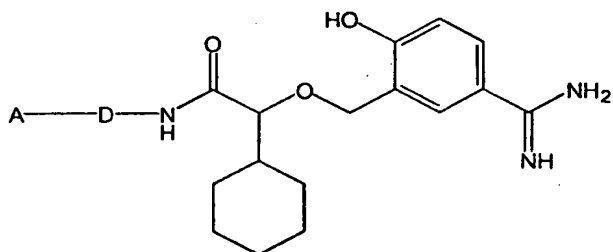
Table 13



Formula XIV

A	D	A	D

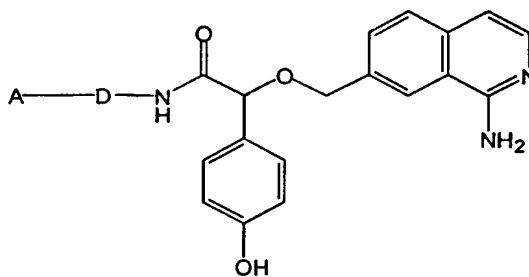
Table 14



Formula XV

A	D	A	D

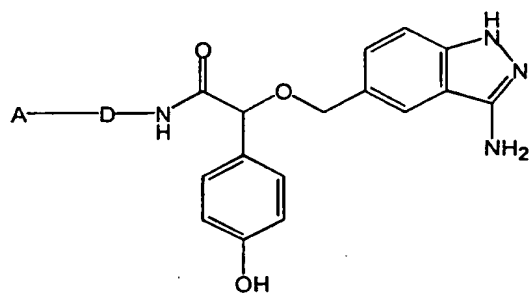
Table 15



Formula XVI

A	D	A	D

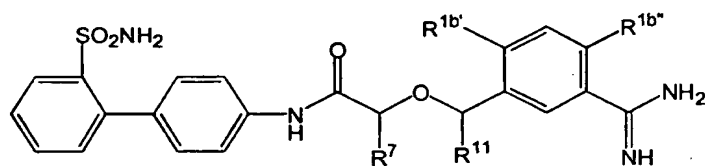
Table 16



Formula XVII

A	D	A	D

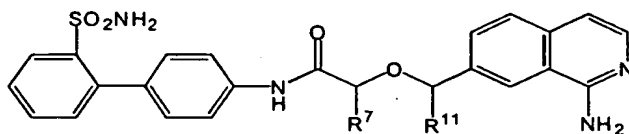
Table 17



Formula XVIII

R ⁷	R ¹¹	R ^{1b'}	R ^{1b''}
H	H	H	H
Me	H	H	OH
		F	H
		-OH	F
		OH	OH
		-NH2	H

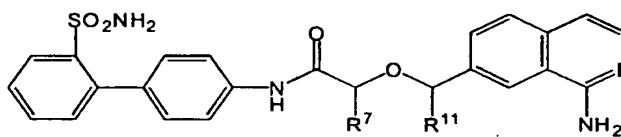
Table 18



Formula XX

R ⁷	R ¹¹	R ⁷	R ¹¹
H	H		
Me	H		

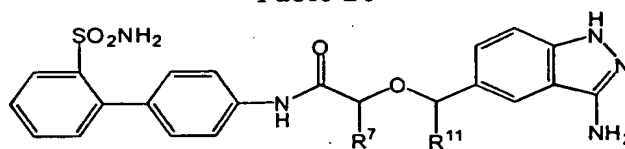
Table 19



Formula XX

R ⁷	R ¹¹	R ⁷	R ¹¹
H	H		
Me	H		

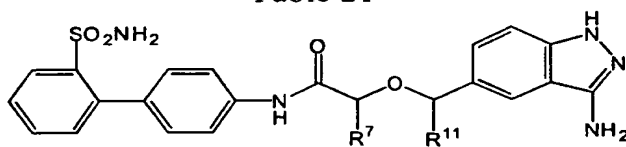
Table 20



Formula XXII

R ⁷	R ¹¹	R ⁷	R ¹¹
H	H		
Me	H		

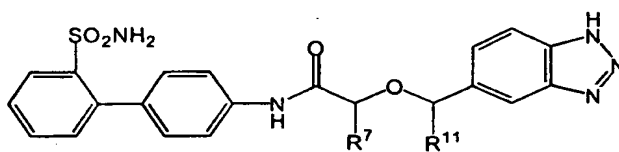
Table 21



Formula XXII

R ⁷	R ¹¹	R ⁷	R ¹¹
H	H		
Me	H		

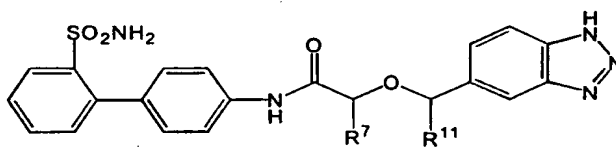
Table 22



Formula XXIV

R ⁷	R ¹¹	R ⁷	R ¹¹
H	H		
Me	H		

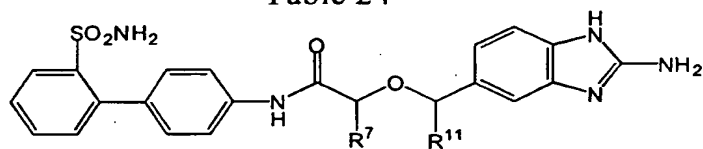
Table 23



Formula XXIV

R ⁷	R ¹¹	R ⁷	R ¹¹
H	H		
Me	H		

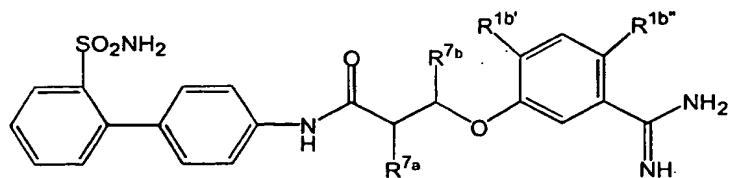
Table 24



Formula XXV

R ⁷	R ¹¹	R ⁷	R ¹¹
H	H		
Me	H		

Table 25



Formula XXVI



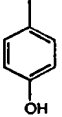


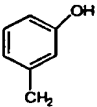

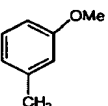
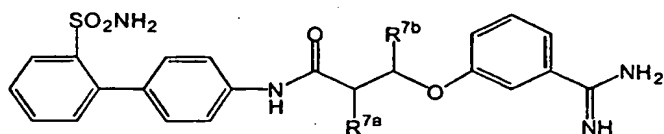
R ^{7a}	R ^{7b}	R ^{1b'}	R ^{1b''}
H	H	H	H
Me	H	H	OH
		F	H
		-OH	F
		OH	OH
		-NH ₂	H

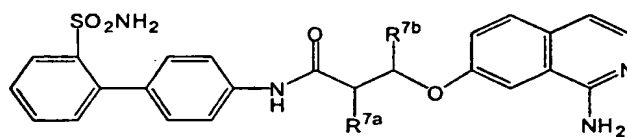
Table 26



Formula XXVII

R ^{7a}	R ^{7b}	R ^{7a}	R ^{7b}
H	H		
Me	H		

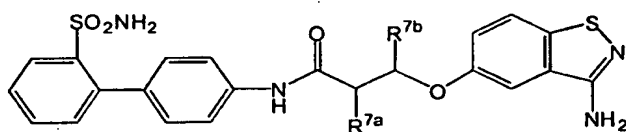
Table 27



Formula XXVIII

R ^{7a}	R ^{7b}	R ^{7a}	R ^{7b}
H	H		
Me	H		

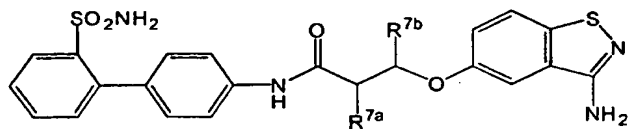
Table 28



Formula XXX

R ^{7a}	R ^{7b}	R ^{7a}	R ^{7b}
H	H		
Me	H		

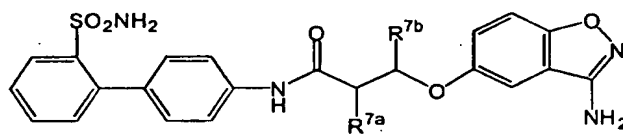
Table 29



Formula XXX

R ^{7a}	R ^{7b}	R ^{7a}	R ^{7b}
H	H		
Me	H		

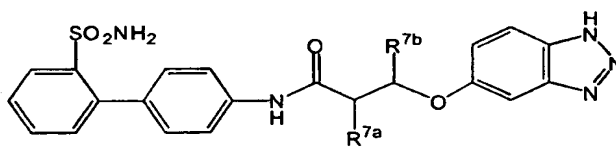
Table 30



Formula XXXI

R ^{7a}	R ^{7b}	R ^{7a}	R ^{7b}
H	H		
Me	H		

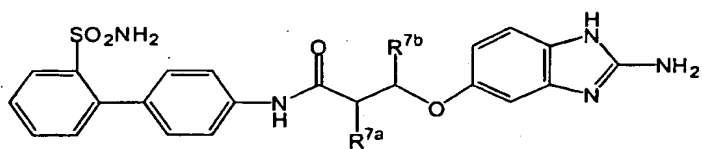
Table 31



Formula XXXII

R ^{7a}	R ^{7b}	R ^{7a}	R ^{7b}
H	H		
Me	H		

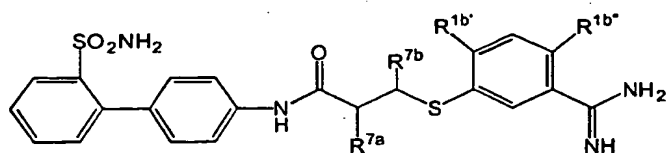
Table 32



Formula XXXIII

R ^{7a}	R ^{7b}	R ^{7a}	R ^{7b}
H	H		
Me	H		

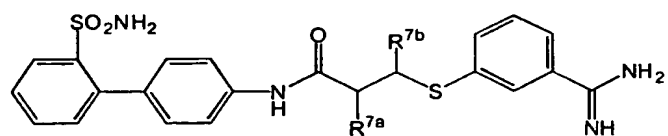
Table 33



Formula XXXIV

R ^{7a}	R ^{7b}	R ^{1b'}	R ^{1b''}
H	H	H	H
Me	H	H	OH
		F	H
		-OH	F
		OH	OH
		-NH ₂	H
-NH ₂	Me	H	F
-NHAc	Me	H	H
NHSO ₂ Me	Me	H	H

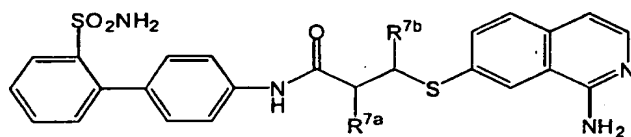
Table 34



Formula XXXV

R ^{7a}	R ^{7b}
H	H
Me	H
-NH ₂	Me
-NHAc	Me
NHSO ₂ Me	Me

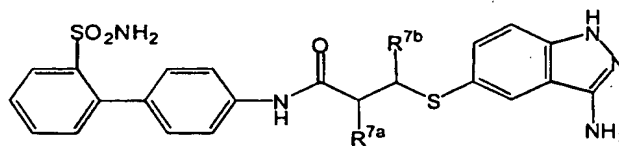
Table 35



Formula XXXVI

R ^{7a}	R ^{7b}
H	H
Me	H
-NH ₂	Me
-NHAc	Me
NHSO ₂ Me	Me

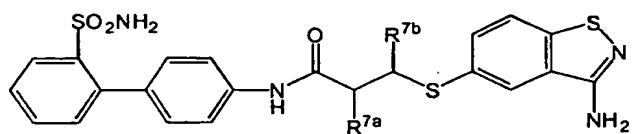
Table 36



Formula XXXVII

R ^{7a}	R ^{7b}
H	H
Me	H
-NH ₂	Me
-NHAc	Me
NHSO ₂ Me	Me

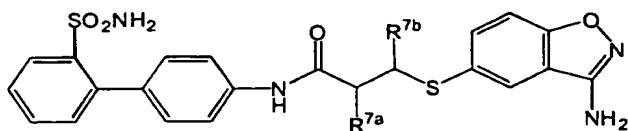
Table 37



Formula XXXVIII

R ^{7a}	R ^{7b}
H	H
Me	H
-NH ₂	Me
-NHAc	Me
NHSO ₂ Me	Me

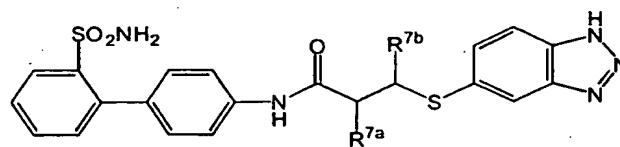
Table 38



Formula XXIX

R ^{7a}	R ^{7b}
H	H
Me	H
-NH ₂	Me
-NHAc	Me
NHSO ₂ Me	Me

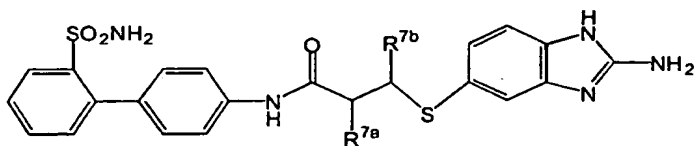
Table 39



Formula XXXX

R ^{7a}	R ^{7b}
H	H
Me	H
-NH ₂	Me
-NHAc	Me
NHSO ₂ Me	Me

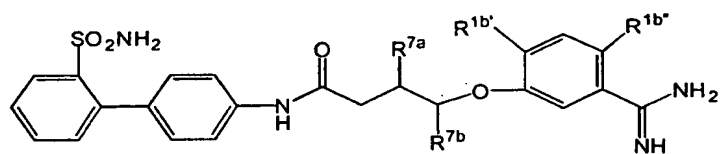
Table 40



Formula XXXXI

R ^{7a}	R ^{7b}
H	H
Me	H
-NH ₂	Me
-NHAc	Me
NHSO ₂ Me	Me

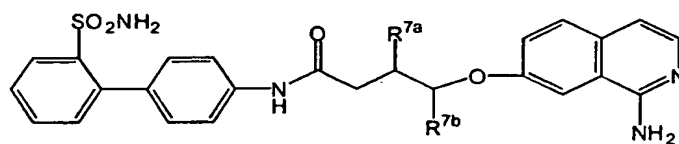
Table 41



Formula XXXXII

R ^{7a}	R ^{7b}	R ^{1b'}	R ^{1b''}
H	H	H	H
-C(=O)NCH ₂ CH ₂ COCH ₃	H	H	OH
		F	H
		-OH	F
		OH	OH
		-NH ₂	H
-COOH	Me	H	F
-COOCH ₃	Me	H	H
-C(=O)N(CH ₃) ₂	Me	H	H

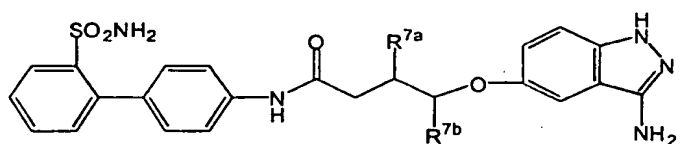
Table 43



Formula XXXIV

R^{7a}	R^{7b}
H	H
$-C(=O)NCH_2CH_2OCH_3$	H
$-COOH$	Me
$-COOC H_3$	Me
$-C(=O)N(CH_3)_2$	Me

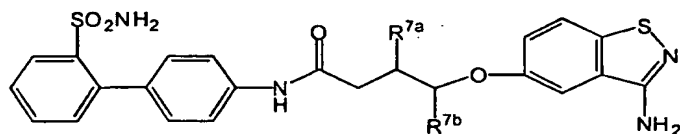
Table 44



Formula XXXXV

R ^{7a}	R ^{7b}
H	H
-C(=O)NCH ₂ CH ₂ OC(=O)CH ₃	H
-COOH	Me
-COOC(=O)CH ₃	Me
-C(=O)N(CH ₃) ₂	Me

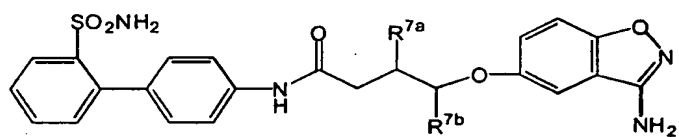
Table 45



Formula XXXXVI

R ^{7a}	R ^{7b}
H	H
-C(=O)NCH ₂ CH ₂ COCH ₃	H
-COOH	Me
-COOCH ₃	Me
-C(=O)N(CH ₃) ₂	Me

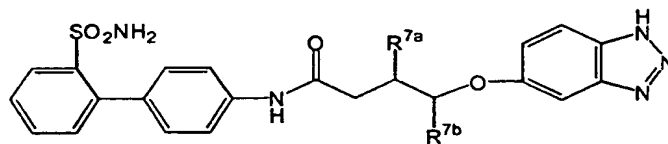
Table 46



Formula XXXXVII

R ^{7a}	R ^{7b}
H	H
-C(=O)NCH ₂ CH ₂ OCH ₃	H
-COOH	Me
-COOCH ₃	Me
-C(=O)N(CH ₃) ₂	Me

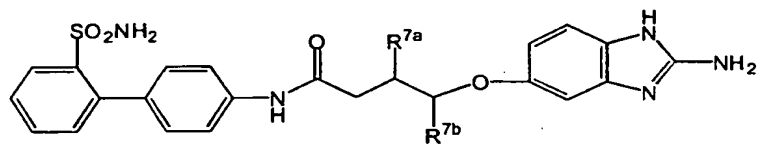
Table 47



Formula XXXXVIII

R ^{7a}	R ^{7b}
H	H
-C(=O)NCH ₂ CH ₂ OCH ₃	H
-COOH	Me
-COOCH ₃	Me
-C(=O)N(CH ₃) ₂	Me

Table 48



Formula XXXIX



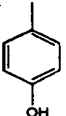


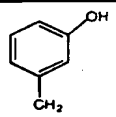
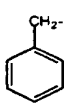
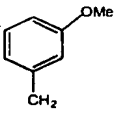
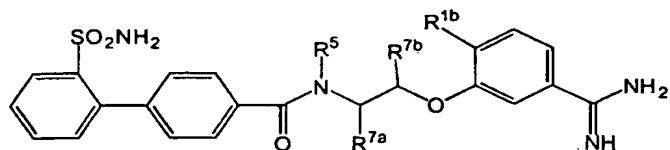
R^{7a}	R^{7b}
H	H
$-C(=O)NCH_2CH_2OCH_3$	H
	
	
	
	
-COOH	Me
-COOCH ₃	Me
$-C(=O)N(CH_3)_2$	Me

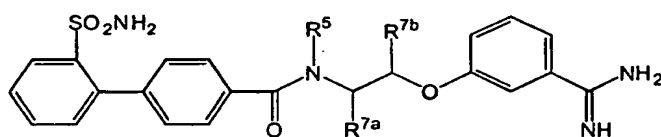
Table 49



Formula L

R ⁵	R ^{7a}	R ^{7b}	R ^{1b}
H	H	H	H
Me	Me	H	H
		Me	F
		Bn	OH
			OMe
			OBn
H	-CH ₂ COOH		OCH ₂ COOH
Me	-CH ₂ CH ₂ COOMe		OCH ₂ CH ₂ OMe
Bn	-CH ₂ CH ₂ CONMe ₂		OH

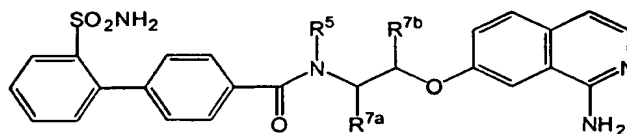
Table 50



Formula LI

R ⁵	R ^{7a}	R ^{7b}
H	H	H
Me	Me	H
		Me
		Bn
H	-CH ₂ OOH	
Me	-CH ₂ CH ₂ COOMe	
Bn	-CH ₂ CH ₂ CONMe ₂	

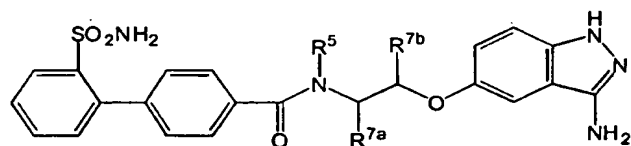
Table 51



Formula LII

R ⁵	R ^{7a}	R ^{7b}
H	H	H
Me	Me	H
		Me
		Bn
H	-CH ₂ COOH	
Me	-CH ₂ CH ₂ COOMe	
Bn	-CH ₂ CH ₂ CONMe ₂	

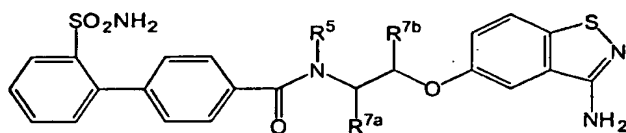
Table 52



Formula LIII

R ⁵	R ^{7a}	R ^{7b}
H	H	H
Me	Me	H
		Me
		Bn
H	-CH ₂ COOH	
Me	-CH ₂ CH ₂ COOMe	
Bn	-CH ₂ CH ₂ CONMe ₂	

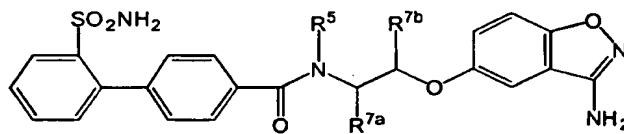
Table 53



Formula LIV

R ⁵	R ^{7a}	R ^{7b}
H	H	H
Me	Me	H
		Me
		Bn
H	-CH ₂ OOH	
Me	-CH ₂ CH ₂ COOMe	
Bn	-CH ₂ CH ₂ CONMe ₂	

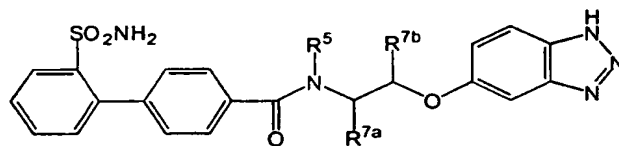
Table 54



Formula LV

R ⁵	R ^{7a}	R ^{7b}
H	H	H
Me	Me	H
		Me
		Bn
H	-CH ₂ COOH	
Me	-CH ₂ CH ₂ COOMe	
Bn	-CH ₂ CH ₂ CONMe ₂	

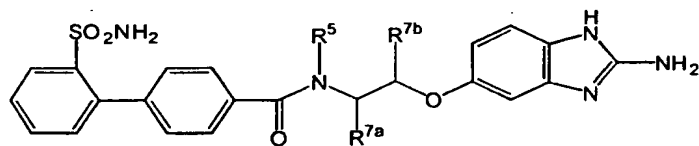
Table 55



Formula LVI

R ⁵	R ^{7a}	R ^{7b}
H	H	H
Me	Me	H
		Me
		Bn
H	-CH ₂ OOH	
Me	-CH ₂ CH ₂ COOMe	
Bn	-CH ₂ CH ₂ CONMe ₂	

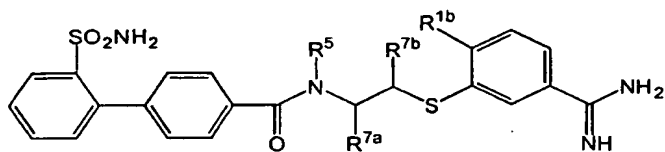
Table 56



Formula LVII

R ⁵	R ^{7a}	R ^{7b}
H	H	H
Me	Me	H
		Me
		Bn
H	-CH ₂ COOH	
Me	-CH ₂ CH ₂ COOMe	
Bn	-CH ₂ CH ₂ CONMe ₂	

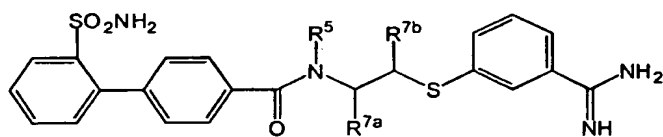
Table 57



Formula LVIII

R ⁵	R ^{7a}	R ^{7b}	R ^{1b}
H	H	H	H
Me	Me	H	H
		Me	F
		Bn	OH
			OMe
			OBn
H	-CH ₂ OOH		OCH ₂ COOH
Me	-CH ₂ CH ₂ COOMe		OCH ₂ CH ₂ OMe
Bn	-CH ₂ CH ₂ CONMe ₂		OH

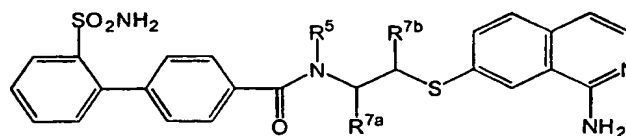
Table 58



Formula LIX

R ⁵	R ^{7a}	R ^{7b}
H	H	H
Me	Me	H
		Me
		Bn
H	-CH ₂ COOH	
Me	-CH ₂ CH ₂ COOMe	
Bn	-CH ₂ CH ₂ CONMe ₂	

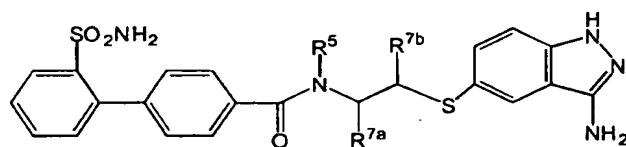
Table 59



Formula LX

R ⁵	R ^{7a}	R ^{7b}
H	H	H
Me	Me	H
		Me
		Bn
H	-CH ₂ OOH	
Me	-CH ₂ CH ₂ COOMe	
Bn	-CH ₂ CH ₂ CONMe ₂	

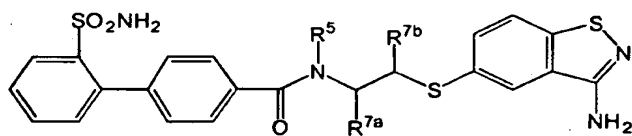
Table 60



Formula LXI

R ⁵	R ^{7a}	R ^{7b}
H	H	H
Me	Me	H
		Me
		Bn
H	-CH ₂ COOH	
Me	-CH ₂ CH ₂ COOMe	
Bn	-CH ₂ CH ₂ CONMe ₂	

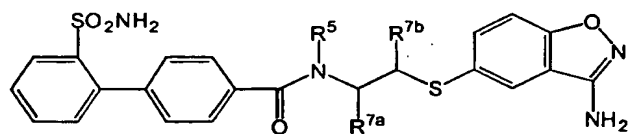
Table 61



Formula LXII

R ⁵	R ^{7a}	R ^{7b}
H	H	H
Me	Me	H
		Me
		Bn
H	-CH ₂ COOH	
Me	-CH ₂ CH ₂ COOMe	
Bn	-CH ₂ CH ₂ CONMe ₂	

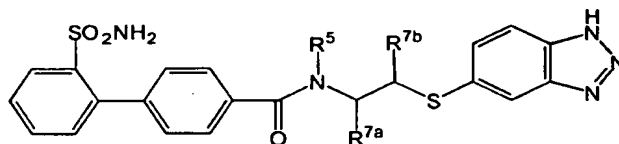
Table 62



Formula LXIII

R ⁵	R ^{7a}	R ^{7b}
H	H	H
Me	Me	H
		Me
		Bn
H	-CH ₂ OOH	
Me	-CH ₂ CH ₂ COOMe	
Bn	-CH ₂ CH ₂ CONMe ₂	

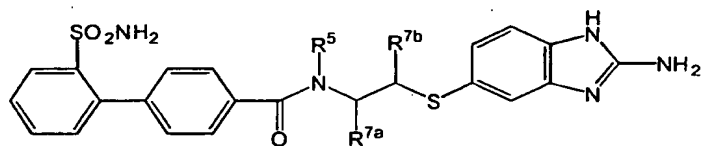
Table 63



Formula LXIV

R ⁵	R ^{7a}	R ^{7b}
H	H	H
Me	Me	H
		Me
		Bn
H	-CH ₂ COOH	
Me	-CH ₂ CH ₂ COOMe	
Bn	-CH ₂ CH ₂ CONMe ₂	

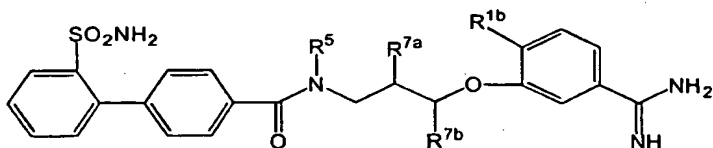
Table 64



Formula LXV

R ⁵	R ^{7a}	R ^{7b}
H	H	H
Me	Me	H
		Me
		Bn
H	-CH ₂ COOH	
Me	-CH ₂ CH ₂ COOMe	
Bn	-CH ₂ CH ₂ CONMe ₂	

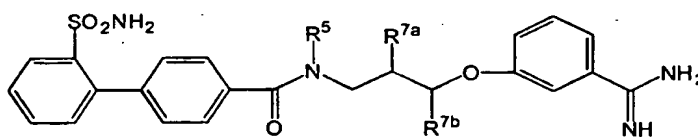
Table 65



Formula LXVI

R ⁵	R ^{7a}	R ^{7b}	R ^{1b}
H	H	H	H
Me	Me	H	H
		Me	F
		Bn	OH
			OMe
			OBn
H	-CH ₂ COOH		OCH ₂ COOH
Me	-CH ₂ CH ₂ COOMe		OCH ₂ CH ₂ OMe
Bn	-CH ₂ CH ₂ CONMe ₂		OH

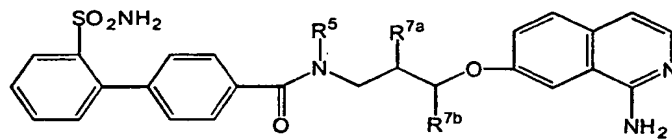
Table 66



Formula LXVII

R ⁵	R ^{7a}	R ^{7b}
H	H	H
Me	Me	H
		Me
		Bn
H	-CH ₂ COOH	
Me	-CH ₂ CH ₂ COOMe	
Bn	-CH ₂ CH ₂ CONMe ₂	

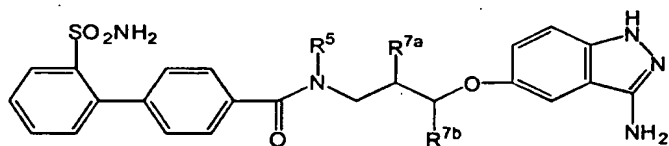
Table 67



Formula LXVIII

R ⁵	R ^{7a}	R ^{7b}
H	H	H
Me	Me	H
		Me
		Bn
H	-CH ₂ COOH	
Me	-CH ₂ CH ₂ COOMe	
Bn	-CH ₂ CH ₂ CONMe ₂	

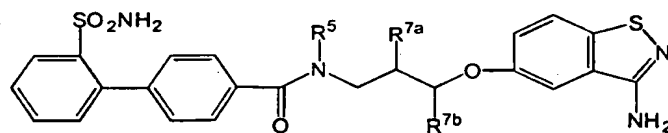
Table 68



Formula LXVIX

R ⁵	R ^{7a}	R ^{7b}
H	H	H
Me	Me	H
		Me
		Bn
H	-CH ₂ COOH	
Me	-CH ₂ CH ₂ COOMe	
Bn	-CH ₂ CH ₂ CONMe ₂	

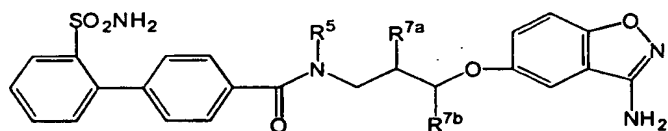
Table 69



Formula LXX

R ⁵	R ^{7a}	R ^{7b}
H	H	H
Me	Me	H
		Me
		Bn
H	-CH ₂ COOH	
Me	-CH ₂ CH ₂ COOMe	
Bn	-CH ₂ CH ₂ CONMe ₂	

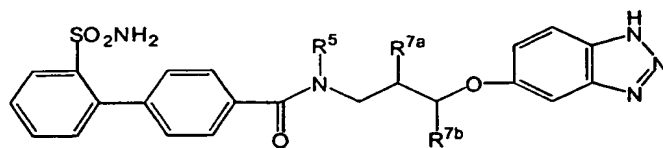
Table 70



Formula LXXI

R ⁵	R ^{7a}	R ^{7b}
H	H	H
Me	Me	H
		Me
		Bn
H	-CH ₂ COOH	
Me	-CH ₂ CH ₂ COOMe	
Bn	-CH ₂ CH ₂ CONMe ₂	

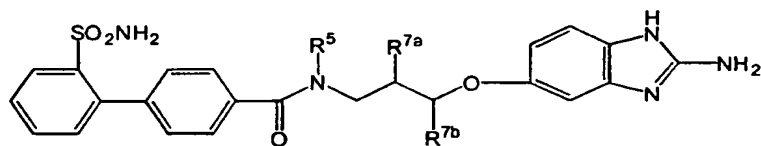
Table 71



Formula LXXII

R ⁵	R ^{7a}	R ^{7b}
H	H	H
Me	Me	H
		Me
		Bn
H	-CH ₂ COOH	
Me	-CH ₂ CH ₂ COOMe	
Bn	-CH ₂ CH ₂ CONMe ₂	

Table 72



Formula LXXIII

R ⁵	R ^{7a}	R ^{7b}
H	H	H
Me	Me	H
		Me
		Bn
H	-CH ₂ COOH	
Me	-CH ₂ CH ₂ COOMe	
Bn	-CH ₂ CH ₂ CONMe ₂	

Table 73

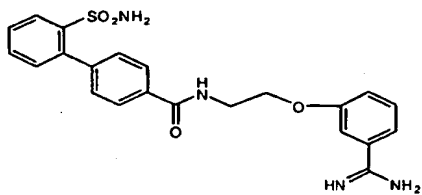
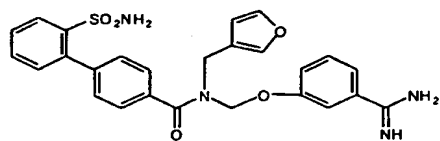
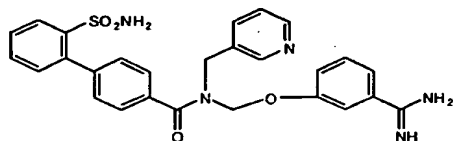
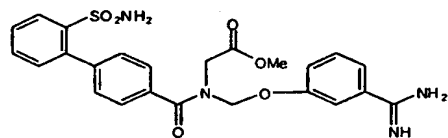
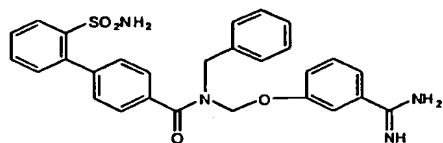
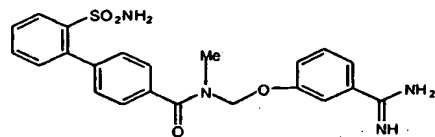
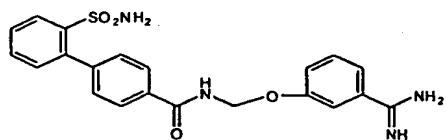
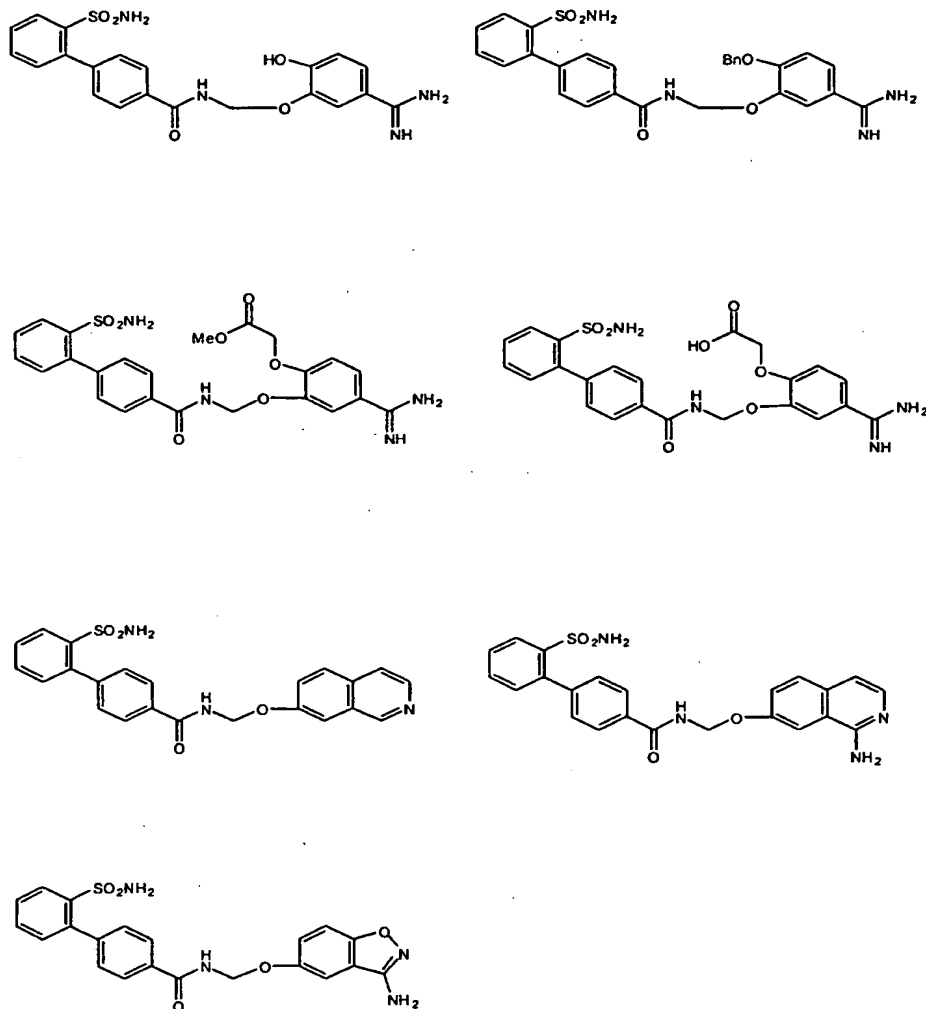


Table 74



This invention also encompasses all pharmaceutically acceptable isomers, salts, hydrates and solvates of the compounds of formulas I, II and III. In addition, the compounds of formulas I, II and III can exist in various isomeric and tautomeric forms, and all such forms are meant to be included in the invention, along with pharmaceutically acceptable salts, hydrates and solvates of such isomers and tautomers.

The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, the free acid or free base form of a compound of one of the formulas above can be reacted with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

15 Prodrug Derivatives of Compounds

This invention also encompasses prodrug derivatives of the compounds contained herein. The term "prodrug" refers to a pharmacologically inactive derivative of a parent drug molecule that requires biotransformation, either spontaneous or enzymatic, within the organism to release the active drug. Prodrugs are variations or derivatives of the compounds of this invention which have groups cleavable under metabolic conditions. Prodrugs become the compounds of the invention which are pharmaceutically active *in vivo*, when they undergo solvolysis under physiological conditions or undergo enzymatic degradation. Prodrug compounds of this invention may be called single, double, triple etc., depending on the number of biotransformation steps required to release the active drug within the organism, and indicating the number of functionalities present in a precursor-type form. Prodrug forms often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985 and Silverman, The Organic Chemistry of Drug Design and Drug Action, pp. 352-401, Academic Press, San Diego, CA, 1992). Prodrugs commonly known in the art include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acids with a suitable alcohol, or amides prepared by reaction of the parent acid compound with an amine, or basic groups reacted to form an acylated base

derivative. Moreover, the prodrug derivatives of this invention may be combined with other features herein taught to enhance bioavailability:

As mentioned above, the compounds of this invention find utility as therapeutic agents for disease states in mammals which have disorders of coagulation such as in the treatment or prevention of unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, thrombotic stroke, embolic stroke, disseminated intravascular coagulation including the treatment of septic shock, deep venous thrombosis in the prevention of pulmonary embolism or the treatment of reocclusion or restenosis of reperfused coronary arteries. Further, these compounds are useful for the treatment or prophylaxis of those diseases which involve the production and/or action of factor Xa/prothrombinase complex. This includes a number of thrombotic and prothrombotic states in which the coagulation cascade is activated which include but are not limited to, deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, thromboembolic complications of surgery and peripheral arterial occlusion.

Accordingly, a method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprises administering to the mammal a therapeutically effective amount of a compound of this invention. In addition to the disease states noted above, other diseases treatable or preventable by the administration of compounds of this invention include, without limitation, occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty, thrombus formation in the venous vasculature, disseminated intravascular coagulopathy, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure, hemorrhagic stroke, renal dialysis, blood oxygenation, and cardiac catheterization.

The compounds of the invention also find utility in a method for inhibiting the coagulation biological samples, which comprises the administration of a compound of the invention.

The compounds of the present invention may also be used in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this invention may be coadministered along with other compounds

typically prescribed for these conditions according to generally accepted medical practice such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of the present invention may act in a synergistic fashion to prevent reocclusion following a successful thrombolytic therapy and/or reduce the time to reperfusion. These compounds may also allow for reduced doses of the thrombolytic agents to be used and therefore minimize potential hemorrhagic side-effects. The compounds of this invention can be utilized *in vivo*, ordinarily in mammals such as primates, (e.g. humans), sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

The biological properties of the compounds of the present invention can be readily characterized by methods that are well known in the art, for example by the *in vitro* protease activity assays and *in vivo* studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters, such as are illustrated in the examples.

Diagnostic applications of the compounds of this invention will typically utilize formulations in the form of solutions or suspensions. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages

and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as
5 polyvinylpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrans, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethyleneglycol.

10 Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will
15 be 3-11, more preferably 5-9 and most preferably 7-8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as orally, intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically,
20 rectally, nasally, transdermally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable
25 polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

The compounds of the invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of
30 lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers.

Such polymers can include polyvinylpyrrolidinone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, compounds of the invention may be coupled to a class of biodegradable polymers
5 useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyeppilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be
10 formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

15 Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will be influenced by the route of administration, the therapeutic objectives and the condition of the patient. For
20 injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each compound by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic
25 effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be readily determined by one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

30 The compounds of the invention can be administered orally or parenterally in an effective amount within the dosage range of about 0.1 to 100 mg/kg, preferably about 0.5 to 50 mg/kg and more preferably about 1 to 20 mg/kg on a regimen in a single or 2 to 4 divided daily doses and/or continuous infusion.

35 Typically, about 5 to 500 mg of a compound or mixture of compounds of

this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a
5 suitable dosage in the range indicated is obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like are binders such as acacia, corn starch or gelatin, and excipients such as microcrystalline cellulose, disintegrating agents like corn starch or alginic acid,
10 lubricants such as magnesium stearate, sweetening agents such as sucrose or lactose, or flavoring agents. When a dosage form is a capsule, in addition to the above materials it may also contain liquid carriers such as water, saline, or a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be
15 formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

20 Preparation of Compounds

The compounds of the present invention may be synthesized by either solid or liquid phase methods described and referenced in standard textbooks, or by a combination of both methods. These methods are well known in the art. See,
25 Bodanszky, "The Principles of Peptide Synthesis", Hafner, *et al.*, Eds., Springer-Verlag, Berlin, 1984.

Starting materials used in any of these methods are commercially available from chemical vendors such as Aldrich, Sigma, Nova Biochemicals, Bachem
30 Biosciences, and the like, or may be readily synthesized by known procedures.

Reactions are carried out in standard laboratory glassware and reaction vessels under reaction conditions of standard temperature and pressure, except where otherwise indicated.

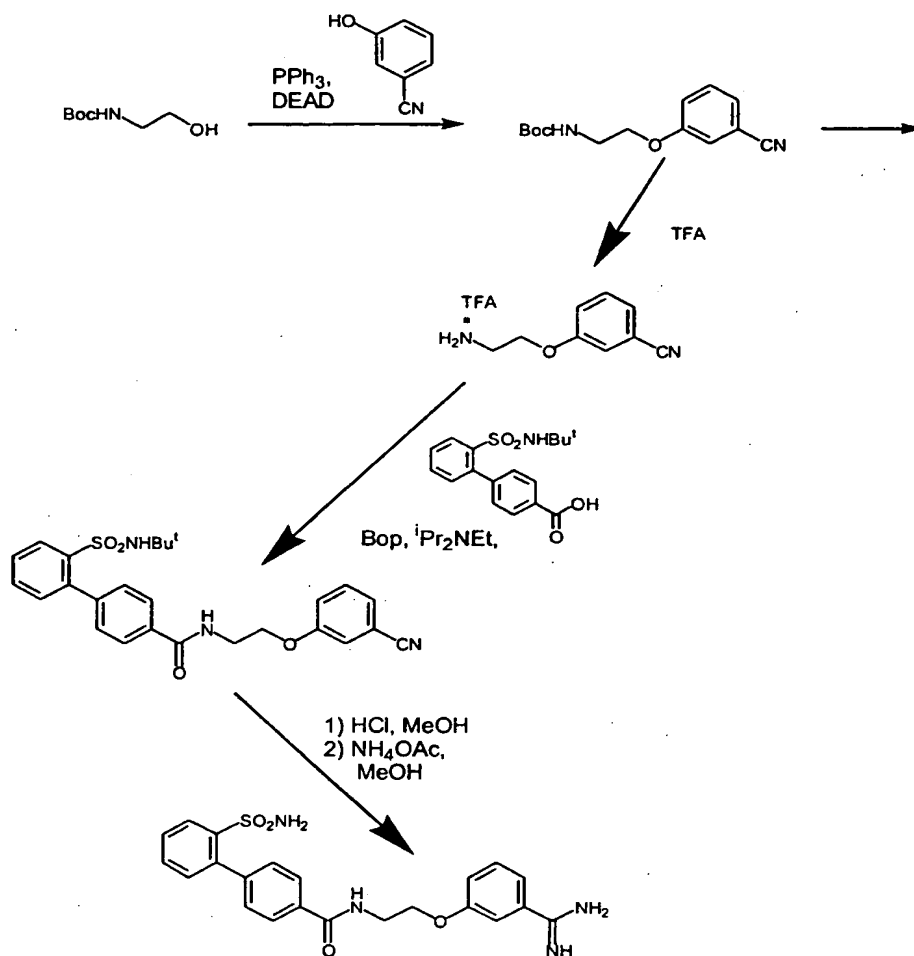
35

- During the synthesis of these compounds, the functional groups of the amino acid derivatives used in these methods are protected by blocking groups to prevent cross reaction during the coupling procedure. Examples of suitable blocking groups and their use are described in "The Peptides: Analysis, Synthesis, Biology",
- 5 Academic Press, Vol. 3 (Gross, *et al.*, Eds., 1981) and Vol. 9 (1987), the disclosures of which are incorporated herein by reference.

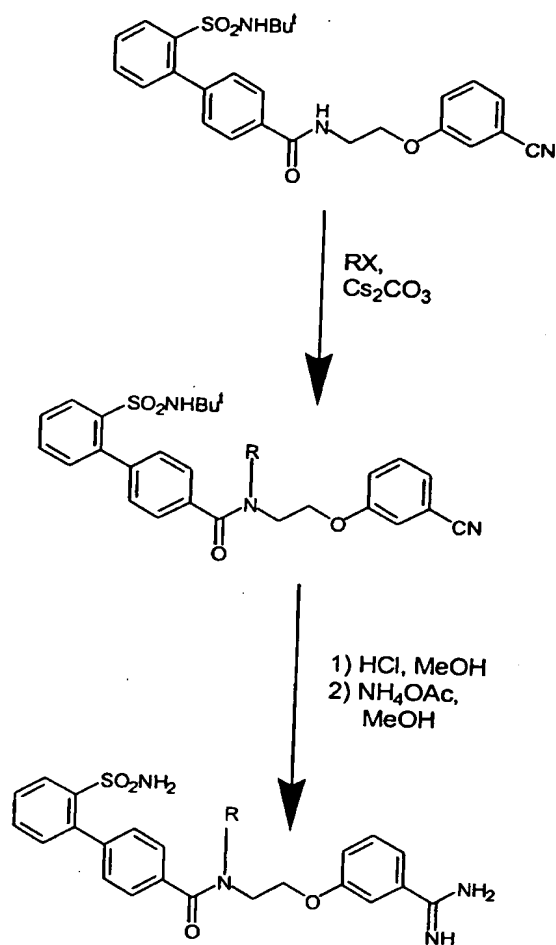
- Non-limiting exemplary synthesis schemes are outlined directly below, and specific steps are described in the Examples. The reaction products are isolated and
- 10 purified by conventional methods, typically by solvent extraction into a compatible solvent. The products may be further purified by column chromatography or other appropriate methods.

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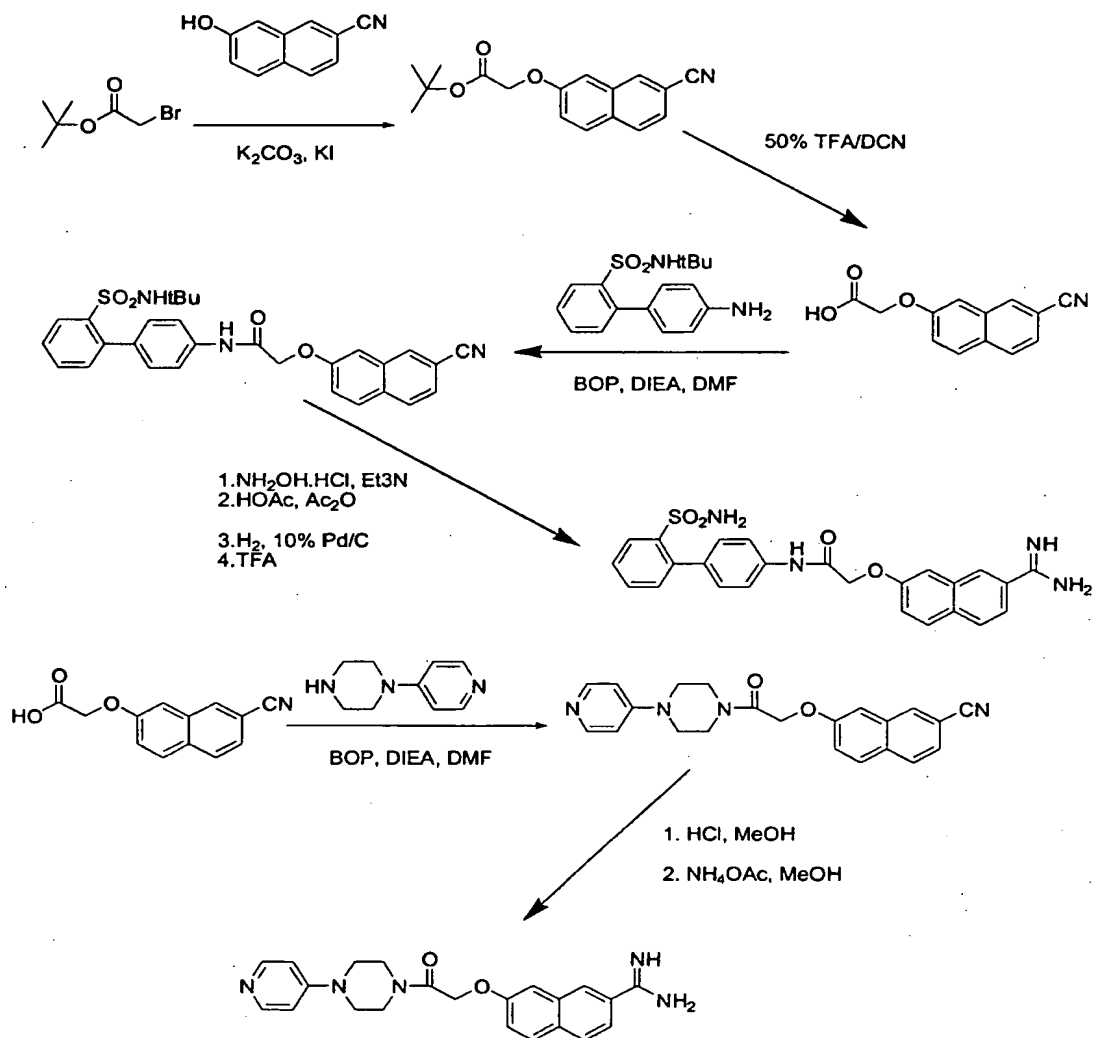
Scheme 1

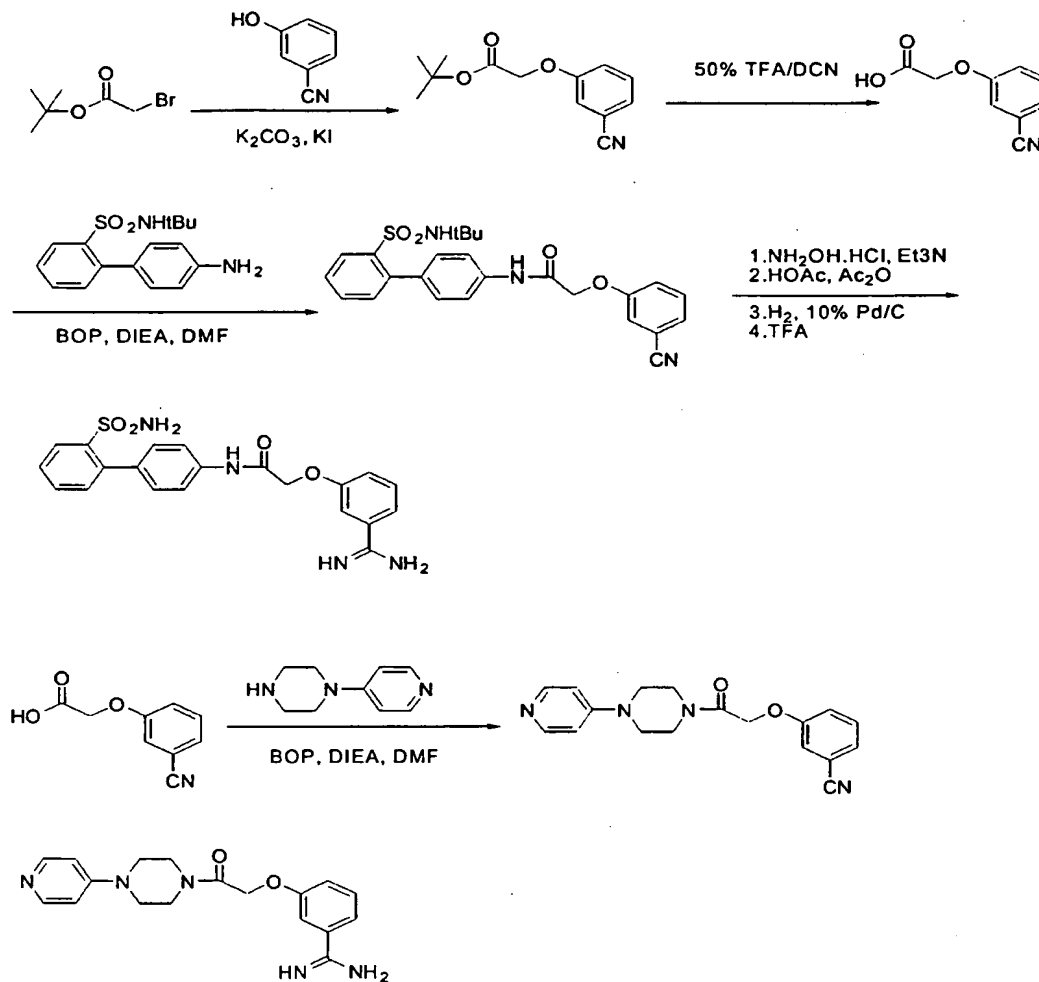


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Scheme 2

Scheme 3



Scheme 4

5

Compositions and Formulations

The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts

are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, reaction of the free acid or free base form of a compound of the structures recited above with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

Diagnostic applications of the compounds of this invention will typically utilize formulations such as solution or suspension. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with

- physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinylpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrans, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethyleneglycol.
- 15 Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will
- 20 be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as intravenously (bolus and/or infusion), subcutaneously,
- 25 intramuscularly, colonically, rectally, nasally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders,

aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber
5 or other polymers commercially available.

The compounds of this invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

10 The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-
15 propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the factor Xa inhibitors of this invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon
20 caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will naturally be influenced by the route of administration, the therapeutic objectives, and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each inhibitor by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be within the ambit of one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

A typical dosage might range from about 0.001 mg/kg to about 1000 mg/kg, preferably from about 0.01 mg/kg to about 100 mg/kg, and more preferably from about 0.10 mg/kg to about 20 mg/kg. Advantageously, the compounds of this invention may be administered several times daily, and other dosage regimens may also be useful.

Typically, about 0.5 to 500 mg of a compound or mixture of compounds of this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical

practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like are a binder such as acacia, corn starch or gelatin, and excipient such as microcrystalline cellulose, a disintegrating agent like corn starch or alginic acid, a lubricant such as magnesium stearate, a sweetening agent such as sucrose or lactose, or a flavoring agent. When a dosage form is a capsule, in addition to the above materials it may also contain a liquid carrier such as water, saline, a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

In practicing the methods of this invention, the compounds of this invention may be used alone or in combination, or in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this inventions may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice, such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of this invention can be utilized in vivo, ordinarily in mammals such as primates, such as humans, sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

The preferred compounds of the present invention are characterized by their ability to inhibit thrombus formation with acceptable effects on classical measures of coagulation parameters, platelets and platelet function, and acceptable levels of bleeding complications associated with their use. Conditions characterized by
5 undesired thrombosis would include those involving the arterial and venous vasculature.

With respect to the coronary arterial vasculature, abnormal thrombus formation characterizes the rupture of an established atherosclerotic plaque which is the major cause of acute myocardial infarction and unstable angina, as well as also
10 characterizing the occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA).

With respect to the venous vasculature, abnormal thrombus formation characterizes the condition observed in patients undergoing major surgery in the lower extremities or the abdominal area who often suffer from thrombus formation
15 in the venous vasculature resulting in reduced blood flow to the affected extremity and a predisposition to pulmonary embolism. Abnormal thrombus formation further characterizes disseminated intravascular coagulopathy commonly occurs within both vascular systems during septic shock, certain viral infections and cancer, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation
20 which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure.

The compounds of this present invention, selected and used as disclosed herein, are believed to be useful for preventing or treating a condition characterized by undesired thrombosis, such as (a) the treatment or prevention of any
25 thrombotically mediated acute coronary syndrome including myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-

thrombolytic therapy or post-coronary angioplasty, (b) the treatment or prevention of any thrombotically mediated cerebrovascular syndrome including embolic stroke, thrombotic stroke or transient ischemic attacks, (c) the treatment or prevention of any thrombotic syndrome occurring in the venous system including deep venous

5 thrombosis or pulmonary embolus occurring either spontaneously or in the setting of malignancy, surgery or trauma, (d) the treatment or prevention of any coagulopathy including disseminated intravascular coagulation (including the setting of septic shock or other infection, surgery, pregnancy, trauma or malignancy and whether associated with multi-organ failure or not), thrombotic thrombocytopenic purpura,

10 thromboangiitis obliterans, or thrombotic disease associated with heparin induced thrombocytopenia, (e) the treatment or prevention of thrombotic complications associated with extracorporeal circulation (e.g. renal dialysis, cardiopulmonary bypass or other oxygenation procedure, plasmapheresis), (f) the treatment or prevention of thrombotic complications associated with instrumentation (e.g. cardiac

15 or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve), and (g) those involved with the fitting of prosthetic devices.

Anticoagulant therapy is also useful to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus the compounds of this invention can be added to or contacted with any

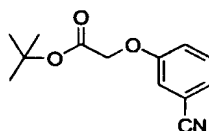
20 medium containing or suspected to contain factor Xa and in which it is desired that blood coagulation be inhibited, e.g., when contacting the mammal's blood with material such as vascular grafts, stents, orthopedic prostheses, cardiac stents, valves and prostheses, extra corporeal circulation systems and the like.

Without further description, it is believed that one of ordinary skill in the art

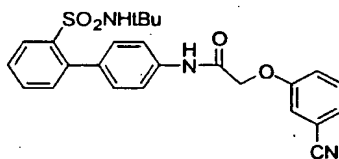
25 can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed

methods. The following working examples therefore, specifically point out preferred embodiments of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

5

EXAMPLESExample 1

To a solution of t-butyl bromoacetate (1.62 mL, 10 mmol), 3-cyanophenol (1.19 g, 10 mmol), potassium carbonate (2.76 g, 20 mmol) in CH₃CN (15 mL) and acetone (5 mL), was added KI (165 mg, 1 mmol). The mixture was heated to reflux for 2 hrs. The mixture was cooled to room temperature and solvent was removed *in vacuo*. Ether and water were added to the mixture and organic layer was washed with 2N NaOH, brine, dried over Na₂SO₄, filtered and the filtrate were concentrated in *vacuo* to give the title compound (2.53 g, 100%). ES-MS (M+H)⁺ = 234.1

Example 2

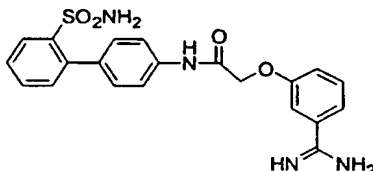
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The compound of example 1 (0.3 mmol) was treated with 50% TFA in DCM (4 mL). The mixture was stirred at room temperature for 30 minutes and solvent evaporated to give a white solid. This was dissolved in DMF (2 mL) and cooled to 0°C. The solution was neutralized with DIEA (87 µL, 0.5 mmol) followed by the addition of compound of example 4 (76 mg, 0.25 mmol) and coupling reagent BOP (132.8 mg, 0.3 mmol). The solution was stirred at room temperature for 15 hours. The reaction mixture was diluted in a mixture of EtOAc/H₂O (10 mL:5mL). The organic layer was washed with sat. NaHCO₃ (2 X 10 mL), sat. NaCl (2 X 10

mL), dried over MgSO_4 , filtered and solvent evaporated to give the crude product. This was purified by silica gel column chromatography using solvent system 50% EtOAc in hexane as eluant to give the title compound (121 mg, 100%). ES-MS $(\text{M}+\text{Na})^+ = 486.15$.

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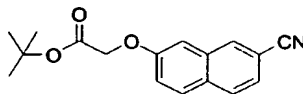
Example 3



A solution of the compound of example 2 (121 mg, 0.26 mmol), hydroxylamine hydrochloride (36.14 mg, 0.52 mmol), TEA (109 μL , 0.78 mmol) in absolute ethanol (4 mL) was heated up to 60°C and stirred for 15 hrs. The solution was cooled and solvent evaporated. The residue was dissolved in AcOH (2 mL). Ac_2O (98.5 μL , 1.04 mmol) was added. The mixture was stirred at room temperature for 50 min. and the solvent evaporated. The residue was dissolved in MeOH (2-3 mL) and 10% Pd/C (catalytic amount) was added. The mixture was hydrogenated under balloon overnight, filtered through Celite to remove the catalyst and the filtrate was evaporated. TFA (2-3 mL) was added to the residue and the mixture was stirred at room temperature for 2-3 hrs. TFA was removed under reduced pressure to give the crude product. The obtained residue was purified by RP-HPLC to give the title compound as a white powder. ES-MS $(\text{M}+\text{H})^+ = 425.1$.

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Example 4



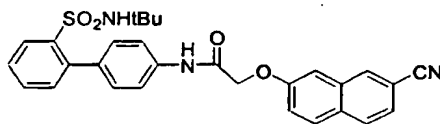
To a solution of t-butyl bromoacetate (1.62 mL, 10 mmol), 7-cyano-2-naphthol (1.69 g, 10 mmol), potassium carbonate (2.76 g, 20 mmol) in CH_3CN (15 mL) and acetone (5 mL), was added KI (165 mg, 1 mmol). The mixture was heated to reflux for 2 hrs. The mixture was cooled to room temperature and solvent was removed *in vacuo*. Ether and water were added to the mixture and organic layer was washed with 2N NaOH, brine, dried over Na_2SO_4 , filtered and the filtrate were

25

concentrated *in vacuo* to give the title compound (2.76 g, 97.5%). ES-MS (M+H)⁺ = 284.1.

Example 5

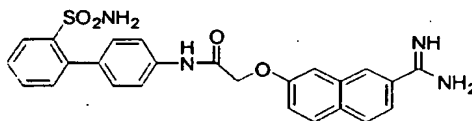
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The compound of example 4 (0.3 mmol) was treated with 50% TFA in DCM (4 mL). The mixture was stirred at room temperature for 30 minutes and solvent evaporated to give a white solid. This was dissolved in DMF (2 mL) and cooled to 0°C. The solution was neutralized with DIEA (87 µL, 0.5 mmol) followed by the addition of compound of example 4 (76 mg, 0.25 mmol) and coupling reagent BOP (132.8 mg, 0.3 mmol). The solution was stirred at room temperature for 15 hours. The reaction mixture was diluted in a mixture of EtOAc/H₂O (10 mL:5mL). The organic layer was washed with sat. NaHCO₃ (2 X 10 mL), sat. NaCl (2 X 10 mL), dried over MgSO₄, filtered and solvent evaporated to give the crude product. This was purified by silica gel column chromatography using solvent system 50% EtOAc in hexane as eluant to give the title compound (142 mg, 92.2%). ES-MS (M+Na)⁺ = 536.15.

Example 6

20

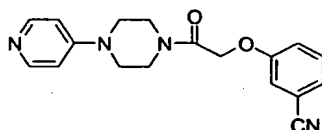


A solution of the compound of example 5 (142 mg, 0.28 mmol), hydroxylamine hydrochloride (38.5 mg, 0.55 mmol), TEA (115 µL, 0.83 mmol) in absolute ethanol (4 mL) was heated up to 60°C and stirred for 15 hrs. The solution was cooled and solvent evaporated. The residue was dissolved in AcOH (2 mL). Ac₂O (104 µL, 1.11 mmol) was added. The mixture was stirred at room temperature for 50 min. and the solvent evaporated. The residue was dissolved in MeOH (2-3 mL) and 10% Pd/C (catalytic amount) was added. The mixture was hydrogenated under balloon overnight, filtered through Celite to remove the catalyst and the filtrate was

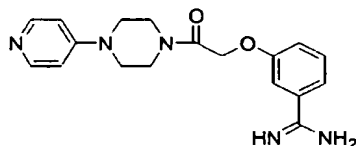
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evaporated. TFA (2-3 mL) was added to the residue and the mixture was stirred at room temperature for 2-3 hrs. TFA was removed under reduced pressure to give the crude product. The obtained residue was purified by RP-HPLC to give the title compound as a white powder. ES-MS (M+H)⁺ = 475.1.

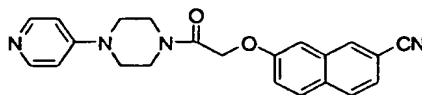
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Example 7

The compound of example 1 (1 mmol) was treated with 50% TFA in DCM (4 mL).
10 The mixture was stirred at room temperature for 30 minutes and solvent evaporated to give a white solid. This was dissolved in DMF (8 mL) and cooled to 0°C. The solution was neutralized with DIEA (349 μ L, 2 mmol) followed by the addition of 1-(4-pyridyl)-piperazine (194 mg, 1.2 mmol) and coupling reagent BOP(531 mg, 1.2 mmol). The solution was stirred at room temperature for 15 hours. The reaction
15 mixture was diluted in a mixture of EtOAc/H₂O (10 mL:5mL). The organic layer was washed with sat. NaHCO₃ (2 X 10 mL), sat. NaCl (2 X 10 mL), dried over MgSO₄, filtered and solvent evaporated to give the title compound (132 mg, 41%). ES-MS (M+H)⁺ = 322.1.

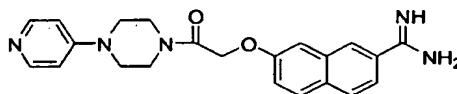
20 Example 8

A solution of the compound of example 7 (132 mg, 0.41 mmol) in MeOH (3 mL) was treated with a stream of HCl gas for 10 min. at 0°C. The resulting solution was
25 capped, stirred at room temperature overnight and evaporated *in vacuo*. The residue was reconstituted in MeOH (3 mL) and the mixture was treated with NH₄OAc (142.6 mg, 1.85 mmol). The reaction mixture was refluxed for 1.5 hrs. and concentrated *in vacuo*. The obtained residue was purified by RP-HPLC to give the title compound as a white powder. ES-MS (M+H)⁺ = 340.1.

Example 9

- 5 The compound of example 4 (1 mmol) was treated with 50% TFA in DCM (4 mL). The mixture was stirred at room temperature for 30 minutes and solvent evaporated to give a white solid. This was dissolved in DMF (8 mL) and cooled to 0°C. The solution was neutralized with DIEA (349 μ L, 2 mmol) followed by the addition of 1-(4-pyridyl)-piperazine (194 mg, 1.2 mmol) and coupling reagent BOP(531 mg, 1.2 mmol). The solution was stirred at room temperature for 15 hours. The reaction mixture was diluted in a mixture of EtOAc/H₂O (10 mL:5mL). The organic layer was washed with sat. NaHCO₃ (2 X 10 mL), sat. NaCl (2 X 10 mL), dried over MgSO₄, filtered and solvent evaporated to give the title compound (209 mg, 56.3%). ES-MS (M+H)⁺ = 372.1.

15

Example 10

- 20 A solution of the compound of example 9 (113 mg, 0.3 mmol) in MeOH (3 mL) was treated with a stream of HCl gas for 10 min. at 0°C. The resulting solution was capped, stirred at room temperature overnight and evaporated *in vacuo*. The residue was reconstituted in MeOH (3 mL) and the mixture was treated with NH₄OAc (115.6 mg, 1.5 mmol). The reaction mixture was refluxed for 1.5 hrs. and concentrated *in vacuo*. The obtained residue was purified by RP-HPLC to give the title compound as a white powder. ES-MS (M+H)⁺ = 390.1.

25

BIOLOGICAL ACTIVITY EXAMPLES

Evaluation of the compounds of this invention is guided by *in vitro* protease activity assays (see below) and *in vivo* studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters.

The compounds of the present invention are dissolved in buffer to give solutions containing concentrations such that assay concentrations range from 0 to 100 μ M. In the assays for thrombin, prothrombinase and factor Xa, a synthetic chromogenic substrate is added to a solution containing test compound and the enzyme of interest and the residual catalytic activity of that enzyme is determined spectrophotometrically. The IC_{50} of a compound is determined from the substrate turnover. The IC_{50} is the concentration of test compound giving 50% inhibition of the substrate turnover. The compounds of the present invention desirably have an IC_{50} of less than 500 nM in the factor Xa assay, preferably less than 200 nM, and more preferred compounds have an IC_{50} of about 100 nM or less in the factor Xa assay. The compounds of the present invention desirably have an IC_{50} of less than 4.0 μ M in the prothrombinase assay, preferably less than 200 nM, and more preferred compounds have an IC_{50} of about 10 nM or less in the prothrombinase assay. The compounds of the present invention desirably have an IC_{50} of greater than 1.0 μ M in the thrombin assay, preferably greater than 10.0 μ M, and more preferred compounds have an IC_{50} of greater than 100.0 μ M in the thrombin assay.

Amidolytic Assays for determining protease inhibition activity

The factor Xa and thrombin assays are performed at room temperature, in 0.02 M Tris-HCl buffer, pH 7.5, containing 0.15 M NaCl. The rates of hydrolysis of the para-nitroanilide substrate S-2765 (Chromogenix) for factor Xa, and the substrate Chromozym TH (Boehringer Mannheim) for thrombin following preincubation of the enzyme with inhibitor for 5 minutes at room temperature, and were determined using the Softmax 96-well plate reader (Molecular Devices), monitored at 405 nm to measure the time dependent appearance of p-nitroaniline.

The prothrombinase inhibition assay is performed in a plasma free system with modifications to the method described by Sinha, U. *et al.*, Thromb. Res., 75, 427-436 (1994). Specifically, the activity of the prothrombinase complex is determined by measuring the time course of thrombin generation using the p-nitroanilide substrate Chromozym TH. The assay consists of preincubation (5 minutes) of selected compounds to be tested as inhibitors with the complex formed from factor Xa (0.5 nM), factor Va (2 nM), phosphatidyl serine:phosphatidyl choline (25:75, 20 μ M) in 20 mM Tris-HCl buffer, pH 7.5, containing 0.15 M NaCl, 5 mM CaCl₂ and 0.1% bovine serum albumin. Aliquots from the complex-inhibitor mixture are added to prothrombin (1 nM) and Chromozym TH (0.1 mM). The rate of substrate cleavage is monitored at 405 nm for two minutes. Eight different concentrations of inhibitor are assayed in duplicate. A standard curve of thrombin generation by an equivalent amount of untreated complex are used for determination of percent inhibition.

15 Antithrombotic Efficacy in a Rabbit Model of Venous Thrombosis

A rabbit deep vein thrombosis model as described by Hollenbach, S. *et al.*, Thromb. Haemost. 71, 357-362 (1994), is used to determine the in-vivo antithrombotic activity of the test compounds. Rabbits are anesthetized with I.M. injections of Ketamine, Xylazine, and Acepromazine cocktail. A standardized protocol consists of insertion of a thrombogenic cotton thread and copper wire apparatus into the abdominal vena cava of the anesthetized rabbit. A non-occlusive thrombus is allowed to develop in the central venous circulation and inhibition of thrombus growth is used as a measure of the antithrombotic activity of the studied compounds. Test agents or control saline are administered through a marginal ear vein catheter. A femoral vein catheter is used for blood sampling prior to and during steady state infusion of test compound. Initiation of thrombus formation begins immediately after advancement of the cotton thread apparatus

into the central venous circulation. Test compounds are administered from time = 30 min to time = 150 min at which the experiment is terminated. The rabbits are euthanized and the thrombus excised by surgical dissection and characterized by weight and histology. Blood samples are analyzed for changes in hematological and coagulation parameters.

5 Effects of Compounds in Rabbit Venous Thrombosis model

Administration of compounds in the rabbit venous thrombosis model demonstrates antithrombotic efficacy at the higher doses evaluated. There are no significant effects of the compound on the aPTT and PT prolongation with the highest dose (100 $\mu\text{g/kg}$ + 2.57 $\mu\text{g/kg/min}$). Compounds have no significant effects on hematological parameters as
10 compared to saline controls. All measurements are an average of all samples after steady state administration of vehicle or (D)-Arg-Gly-Arg-thiazole. Values are expressed as mean \pm SD.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize
15 the compounds of the present invention and practice the claimed methods.

WHAT IS CLAIMED IS:

1. A compound according to the formula:

A-Y-D-E-G-J-Z-L

5 wherein:

A is selected from:

- (a) C₁-C₆-alkyl;
- (b) C₃-C₈-cycloalkyl;
- (c) phenyl, which is independently substituted with 0-2 R¹ substituents;
- 10 (d) naphthyl, which is independently substituted with 0-2 R¹ substituents; and
- (e) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R¹ substituents;

15

R¹ is selected from:

- Halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, -NO₂, (CH₂)_mNR²R³, SO₂NR²R³, SO₂R², CF₃, OR², and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C₁-C₄-alkyl, -CN, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl and -NO₂;

20

R² and R³ are independently selected from the group consisting of:

- H, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, C₀₋₄alkylphenyl and C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂;

30

m is an integer of 0-2;

Y is a member selected from the group consisting of:

a direct link, -C(=O)-, -N(R⁴)-, -C(=O)-N(R⁴)-, -N(R⁴)-C(=O)-, -SO₂-, -O-,
-SO₂-N(R⁴)- and -N(R⁴)-SO₂-;

5 R⁴ is selected from:

H, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl,
C₀₋₄alkylphenyl and C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on
the ring atoms of the phenyl and naphthyl moieties may be independently
replaced with a member selected from the group consisting of halo, C₁₋₄
10 alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN,
and -NO₂;

D is a direct link or is a member selected from the group consisting of:

- (a) phenyl, which is independently substituted with 0-2 R^{1a} substituents;
- (b) naphthyl, which is independently substituted with 0-2 R^{1a}
15 substituents; and
- (c) a monocyclic or fused bicyclic heterocyclic ring system having from
5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are
selected from N, O and S, and wherein the ring system may be
substituted with 0-2 R^{1a} substituents;

20 R^{1a} is selected from:

Halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈
cycloalkyl, -CN, -NO₂, (CH₂)_mNR^{2a}R^{3a}, SO₂NR^{2a}R^{3a}, SO₂R^{2a}, CF₃, OR^{2a},
and a 5-6 membered aromatic heterocyclic system containing from 1-4
heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on
the aromatic heterocyclic system may be independently replaced with a
member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆
25 alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, C₀₋₄alkylphenyl and C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

E is a member selected from the group consisting of:

-N(R⁵)-C(=O)-, -N(R⁵)-C(=O)-CH₂-, -C(=O)-N(R⁵)-, -C(=O)-N(R⁵)-CH₂-,
 -N(R⁵)-C(=O)-N(R⁶)-, -SO₂-N(R⁵)-, -N(R⁵)-SO₂-N(R⁶)- and -N(R⁵)-SO₂-N(R⁶)-C(=O)-;

R⁵ and R⁶ are independently selected from:

H, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, C₀₋₄alkylphenyl, C₀₋₄alkylnaphthyl, C₀₋₄alkylheteroaryl, C₁₋₄alkylCOOH and C₁₋₄alkylCOOC₁₋₄alkyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl, naphthyl and heteroaryl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

G is selected from:

-CR⁷R⁸- and -CR^{7a}R^{8a}-CR^{7b}R^{8b}-

wherein R⁷, R⁸, R^{7a}, R^{8a}, R^{7b} and R^{8b} are independently a member selected from the group consisting of:

hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkyl-C₃₋₈cycloalkyl, C₀₋₄alkylphenyl, C₀₋₄alkylnaphthyl, C₀₋₄alkylimidazolyl, -OR⁹,
 -C₀₋₄alkylCOOR⁹, -C₀₋₄alkylC(=O)NR⁹R¹⁰, -C₀₋₄alkylC(=O)NR⁹-CH₂-CH₂-O-R¹⁰, -C₀₋₄alkylC(=O)NR⁹(-CH₂-CH₂-O-R¹⁰)₂, -N(R⁹)COR¹⁰, -N(R⁹)C(=O)R¹⁰, -N(R⁹)SO₂R¹⁰, and a naturally occurring or synthetic amino acid side chain, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl,

C₃₋₈cycloalkyl, C₀₋₄alkyl-C₃₋₈cycloalkyl, -CN, -OH, -OC₁₋₄alkyl, -OC₁₋₄alkyl-OMe, -OCH₂COOH, and -NO₂;

R⁹ and R¹⁰ are independently selected from:

5 H, C₁₋₄alkyl, C₀₃₋₈cycloalkyl, C₀₋₄alkylphenyl and C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkyl-C₃₋₈cycloalkyl, -CN and -NO₂, and wherein R⁹ and R¹⁰ taken together can form a 5-8 membered heterocyclic ring;

10 J is a member selected from the group consisting of:

-O-, -O-CH(R¹¹)-, -S-, -S(=O)-, -S(=O)₂-, -S-CH(R¹¹)-, -S(=O)-CH(R¹¹)- and -S(=O)₂-CH(R¹¹)-;

R¹¹ is a member selected from the group consisting of:

15 hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkyl-C₃₋₈cycloalkyl, C₀₋₄alkylphenyl, C₀₋₄alkylnaphthyl, C₀₋₄alkylheterocyclic ring having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S, CH₂COOC₁₋₄alkyl, CH₂COOC₁₋₄alkylphenyl and CH₂COOC₁₋₄alkylnaphthyl;

Z is a member selected from the group consisting of:

- 20 (a) phenyl, which is independently substituted with 0-2 R^{1b} substituents;
- (b) naphthyl, which is independently substituted with 0-2 R^{1b} substituents; and
- (c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are
- 25 selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1b} substituents;

R^{1b} is selected from:

30 Halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, -NO₂, NR^{2b}R^{3b}, SO₂NR^{2b}R^{3b}, SO₂R^{2b}, CF₃, OR^{2b}, O-CH₂-OPh, O-CH₂-Ph, O-CH₂-CH₂-OR^{2b}, O-CH₂-COOR^{2b}, N(R^{2b})-CH₂-CH₂-OR^{2b},

N(-CH₂-CH₂-OR^{2b})₂, N(R^{2b})-C(=O)R^{3b}, N(R^{2b})-SO₂-R^{3b}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

R^{2b} and R^{3b} are independently selected from the group consisting of:

H, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, C₀₋₄alkylphenyl and C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

L is selected from:

H, -CN, C(=O)NR¹²R¹³, (CH₂)_nNR¹²R¹³, C(=NR¹²)NR¹²R¹³, NR¹²R¹³, OR¹², -NR¹²C(=NR¹²)NR¹²R¹³, and NR¹²C(=NR¹²)-R¹³;

R¹² and R¹³ are independently selected from:

hydrogen, -OR¹⁴, -NR¹⁴R¹⁵, C₁₋₄alkyl, C₀₋₄alkylphenyl, C₀₋₄alkylnaphthyl, COOC₁₋₄alkyl, COO-C₀₋₄alkylphenyl and COO-C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂;

R¹⁴ and R¹⁵ are independently selected from:

H, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, C₀₋₄alkylphenyl and C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

2. A compound of claim 1, wherein:

5 A is selected from:

- (a) C₁-C₆-alkyl;
- (b) C₃-C₈-cycloalkyl;
- (c) phenyl, which is independently substituted with 0-2 R¹ substituents;
- (d) naphthyl, which is independently substituted with 0-2 R¹ substituents;
- 10 and

- (e) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R¹ substituents;

15 R¹ is selected from:

halo, C₁₋₄alkyl, -CN, (CH₂)_mNR²R³, SO₂NR²R³, SO₂R², CF₃, OR², and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S;

R² and R³ are independently selected from the group consisting of:

20 H, C₁₋₄alkyl and C₀₋₄alkylaryl,

m is an integer of 0-2;

Y is a member selected from the group consisting of:

a direct link, -C(=O)-, -N(R⁴)-, -C(=O)-N(R⁴)-, -N(R⁴)-C(=O)-, -SO₂-, -O-, -SO₂-N(R⁴)- and -N(R⁴)-SO₂-;

25 R⁴ is selected from:

H, C₁₋₄alkyl and C₀₋₄alkylaryl;

D is absent or is a member selected from the group consisting of:

- (a) aryl, which is independently substituted with 0-2 R^{1a} substituents; and
- (b) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1a} substituents;

R^{1a} is selected from:

Halo, C_{1-4} alkyl, -CN, -NO₂, $(CH_2)_mNR^{2a}R^{3a}$, $SO_2NR^{2a}R^{3a}$, SO_2R^{2a} , CF₃, OR^{2a}, and a 5-6 membered aromatic heterocyclic ring containing from 1-4 heteroatoms selected from N, O and S;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, C_{1-4} alkyl and C_{0-4} alkylaryl;

E is a member selected from the group consisting of:

-N(R^5)-C(=O)-, -N(R^5)-C(=O)-CH₂-, -C(=O)-N(R^5)-, -C(=O)-N(R^5)-CH₂-,
 -N(R^5)-C(=O)-N(R^6)-, -SO₂-N(R^5)-, -N(R^5)-SO₂-N(R^6)- and -N(R^5)-SO₂-
 N(R^6)-C(=O)-;

R^5 and R^6 are independently selected from:

H, C_{1-4} alkyl, C_{0-4} alkylaryl, C_{0-4} alkylheteroaryl, C_{1-4} alkylCOOH and C_{1-4} alkylCOOC₁₋₄alkyl;

G is selected from:

-CR⁷R⁸- and -CR^{7a}R^{8a}-CR^{7b}R^{8b}-

wherein R^7 , R^8 , R^{7a} , R^{8a} , R^{7b} and R^{8b} are independently a member selected from the group consisting of:

hydrogen, C_{1-4} alkyl, C_{0-4} alkyl-C₃₋₈cycloalkyl, C_{0-4} alkylaryl, -OR⁹, - C_{0-4} alkylCOOR⁹, - C_{0-4} alkylC(=O)NR⁹R¹⁰, -N(R^9)COR¹⁰,
 N(R^9)C(=O)R¹⁰, -N(R^9)SO₂R¹⁰, and common amino acid side chains;

R^9 and R^{10} are independently selected from:

H, C_{1-4} alkyl and C_{0-4} alkylaryl;

J is a member selected from the group consisting of:

-O-, -O-CH(R¹¹)-, -S- and -S-CH(R¹¹)-;

R¹¹ is a member selected from the group consisting of:

hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylaryl,
 5 C₀₋₄alkylheterocyclics, CH₂COOC₁₋₄alkyl, CH₂COOC₁₋₄alkylaryl;

Z is a member selected from the group consisting of:

(a) aryl, which is independently substituted with 0-2 R^{1b} substituents; and

(b) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to
 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected
 from N, O and S, and wherein the ring system may be substituted with 0-
 2 R^{1b} substituents;

R^{1b} is selected from:

halo, C₁₋₄alkyl, -CN, -NO₂, NR^{2b}R^{3b}, SO₂NR^{2b}R^{3b}, SO₂R^{2b}, CF₃, OR^{2b}, O-
 CH₂-CH₂-OR^{2b}, O-CH₂-COOR^{2b}, N(R^{2b})-CH₂-CH₂-OR^{2b}, N(-CH₂-CH₂-
 15 OR^{2b})₂, N(R^{2b})-C(=O)R^{3b}, N(R^{2b})-SO₂-R^{3b}, and a 5-6 membered aromatic
 heterocyclic ring containing from 1-4 heteroatoms selected from N, O and S;

R^{2b} and R^{3b} are independently selected from the group consisting of:

H, C₁₋₄alkyl and C₀₋₄alkylaryl;

L is selected from:

20 H, -CN, C(=O)NR¹²R¹³, (CH₂)_nNR¹²R¹³, C(=NR¹²)NR¹²R¹³, NR¹²R¹³, OR¹²,
 -NR¹²C(=NR¹²)NR¹²R¹³ and NR¹²C(=NR¹²)-R¹³;

R¹² and R¹³ are independently selected from:

hydrogen, -OR¹⁴, -NR¹⁴R¹⁵, C₁₋₄alkyl, C₀₋₄alkylaryl COOC₁₋₄alkyl, and
 COO-C₀₋₄alkylaryl; and

25 R¹⁴ and R¹⁵ are independently selected from:

H and C₁₋₄alkyl.

3. A compound of claim 1, wherein:

A is selected from:

- (a) phenyl, which is independently substituted with 0-2 R^1 substituents; and
- (b) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^1 substituents;

R^1 is selected from:

halo, $(CH_2)_mNR^2R^3$, $SO_2NR^2R^3$ and SO_2R^2 ;

10 R^2 and R^3 are independently selected from the group consisting of:

H and C_{1-4} alkyl;

Y is a member selected from the group consisting of:

a direct link, $-C(=O)-$, $-SO_2-$ and $-O-$;

D is a member selected from the group consisting of:

- 15 (a) phenyl, which is independently substituted with 0-2 R^{1a} substituents; and
- (b) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1a} substituents;

20 R^{1a} is selected from:

Halo and C_{1-4} alkyl;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, C_{1-4} alkyl, C_{0-4} alkylaryl;

E is a member selected from the group consisting of:

25 $-N(R^5)-C(=O)-$ and $-C(=O)-N(R^5)-$;

R^5 and R^6 are independently selected from:

H, C₁₋₄alkyl, C₀₋₄alkylaryl and C₀₋₄alkylheteroaryl;

G is selected from:



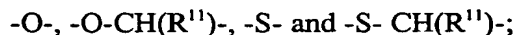
- 5 wherein R⁷, R⁸, R^{7a}, R^{8a}, R^{7b} and R^{8b} are independently a member selected from from the group consisting of:

hydrogen, C₁₋₄alkyl, C₀₋₄alkyl-C₃₋₈cycloalkyl, C₀₋₄alkylaryl, -C₀₋₄alkylCOOR⁹, -OR⁹, -C₀₋₄alkylC(=O)NR⁹R¹⁰, -C₀₋₄alkylC(=O)NR⁹-CH₂-CH₂-O-R¹⁰, -C₀₋₄alkylC(=O)NR⁹(-CH₂-CH₂-O-R¹⁰)₂, -N(R⁹)COR¹⁰, -N(R⁹)C(=O)R¹⁰, -N(R⁹)SO₂R¹⁰, and common amino acid side chains;

- 10 R⁹ and R¹⁰ are independently selected from:

H and C₁₋₄alkyl, wherein the NR⁹R¹⁰ group of R⁷, R⁸, R^{7a}, R^{8a}, R^{7b} and R^{8b} is optionally cyclized to form a 5-8 membered heterocyclic group;

J is a member selected from the group consisting of:



- 15 R¹¹ is a member selected from the group consisting of:

hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, C₀₋₄alkylaryl and a C₀₋₄alkylheterocyclic ring;

Z is a member selected from the group consisting of:

- (a) phenyl, which is independently substituted with 0-2 R^{1b} substituents;
- 20 (b) an aromatic heterocyclic ring having from 5 to 10 ring atoms, wherein 1-4 ring atoms are selected from N, O and S, and wherein the ring may be substituted independently by from 0-2 R^{1b} substituents; and
- (c) a fused aromatic bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected
- 25 from N, O and S, wherein the bicyclic ring system may be substituted with 0-2 R^{1b} substituents;

R^{1b} is selected from:

halo, C_{1-4} alkyl, OH, OBn, $O-CH_2-CH_2-OH$, $O-CH_2-CH_2-OCH_3$, $O-CH_2-COOH$, $O-CH_2-C(=O)-O-CH_3$, NH_2 , $NH-CH_2-CH_2-O-CH_3$, $NH-C(=O)-O-CH_3$, and $NH-SO_2-CH_3$;

L is selected from:

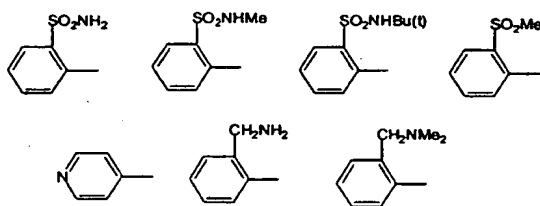
5 H, $C(=O)NR^{12}R^{13}$, $(CH_2)_nNR^{12}R^{13}$ and $C(=NR^{12})NR^{12}R^{13}$; and

R^{12} and R^{13} are independently selected from:

hydrogen and C_{1-4} alkyl.

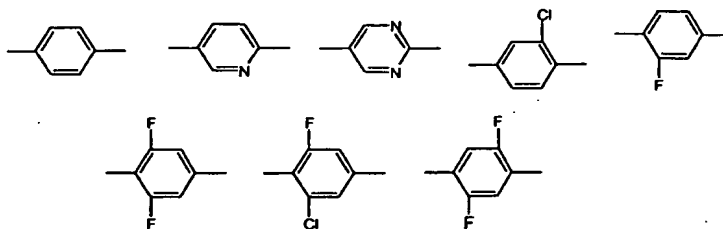
10 4. A compound of claim 1, wherein:

A is a member selected from the group consisting of:



15 Y is a direct link;

D is a member selected from the group consisting of:



5 E is a member selected from the group consisting of:

-C(=O)-NH-, -C(=O)-N(-CH₃)-, C(=O)-N(-Bn)-, -NH-C(=O)-, -N(-CH₃)-C(=O)- and -N(-Bn)C(=O)-;

G is selected from:

10 -CH-(-NH₂)-CH₂-, -CH-(-NH(C(=O)-CH₃))-CH₂-,
-CH-(-NH(C(=O)-Ph))-CH₂-, -CH-(C(=O)-OR⁸)-, -CH(-R⁷)-,
-CH₂-CH(C(=O)-OR⁸)-, and -CH₂-CH(C(=O)-N(-R⁸, -R⁸))-;

R⁷ is a member selected from the group consisting of :

H, phenyl, Bn, -O-loweralkyl, and cyclohexyl;

R⁸ is a member selected from the group consisting of:

15 H, C₁₋₆alkyl, - O-loweralkyl and C₃₋₆cycloalkyl;

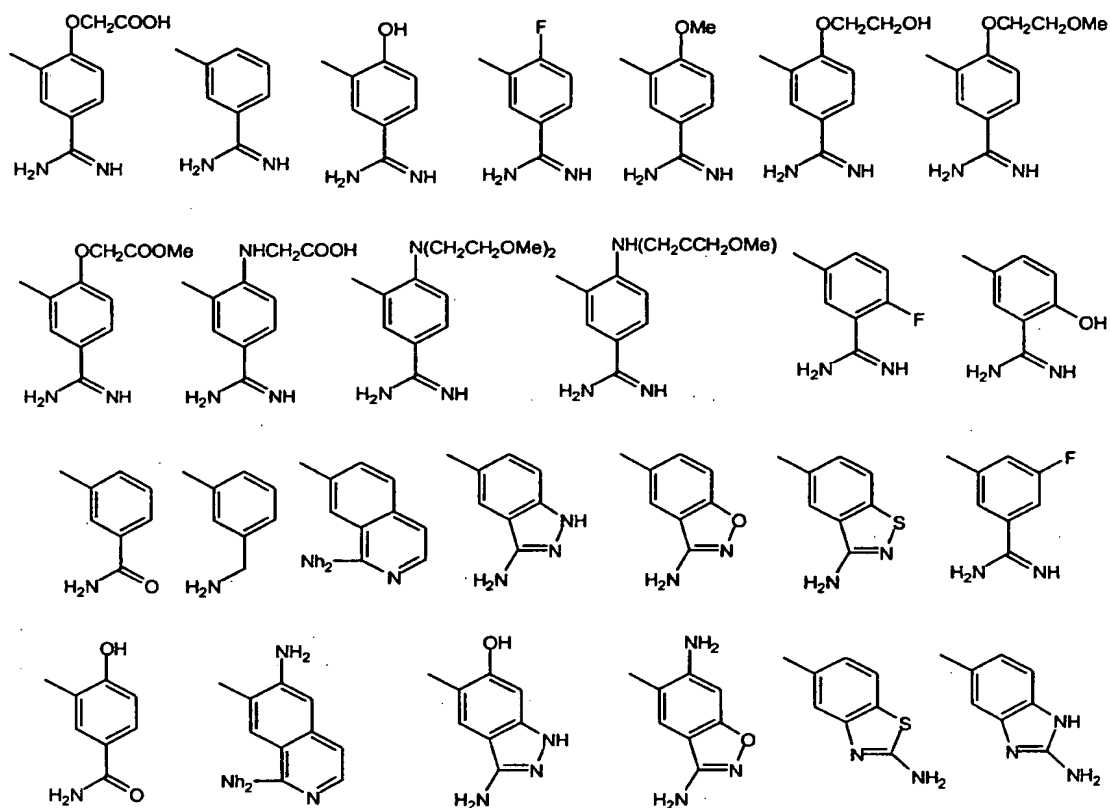
J is a member selected from the group consisting of;

-O-, -O-CH(R¹¹)-, -S- and -S- CH(R¹¹)-;

R¹¹ is a member selected from the group consisting of:

H, methyl, phenyl and benzyl; and

Z and L taken together are a member selected from the group consisting of:



5. A pharmaceutical composition for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising a pharmaceutically acceptable carrier and a compound of claim 1.
6. A pharmaceutical composition for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising a pharmaceutically acceptable carrier and a compound of claim 2.

7. A pharmaceutical composition for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising a pharmaceutically acceptable carrier and a compound of claim 3.
- 5 8. A pharmaceutical composition for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising a pharmaceutically acceptable carrier and a compound of claim 4.
9. A method for preventing or treating a condition in a mammal characterized
10 by undesired thrombosis comprising the step of administering to said mammal a therapeutically effective amount of a compound of claim 1.
10. The method of claim 9, wherein the condition is selected from the group consisting of: acute coronary syndrome, myocardial infarction, unstable angina,
15 refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolus, coagulopathy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis
20 obliterans, thrombotic disease associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation such as cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve, and conditions requiring the fitting of prosthetic devices.

11. A method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising the step of administering to said mammal a therapeutically effective amount of a compound of claim 2.

5 12. The method of claim 11, wherein the condition is selected from the group consisting of: acute coronary syndrome, myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis,
10 deep venous thrombosis, pulmonary embolus, coagulopathy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation such as cardiac or other intravascular
15 catheterization, intra-aortic balloon pump, coronary stent or cardiac valve, and conditions requiring the fitting of prosthetic devices.

13. A method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising the step of administering to said mammal a
20 therapeutically effective amount of a compound of claim 3.

14. The method of claim 13, wherein the condition is selected from the group consisting of: acute coronary syndrome, myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy
25 or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolus, coagulopathy, disseminated

intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation such as cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve, and conditions requiring the fitting of prosthetic devices.

15. A method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising the step of administering to said mammal a therapeutically effective amount of a compound of claim 4.

16. The method of claim 15, wherein the condition is selected from the group consisting of: acute coronary syndrome, myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolus, coagulopathy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation such as cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve, and conditions requiring the fitting of prosthetic devices.

17. A method for inhibiting the coagulation of biological samples comprising the step of administering a compound of claim 1.

18. A method for inhibiting the coagulation biological samples comprising the step of administering a compound of claim 2.

19. A method for inhibiting the coagulation biological samples comprising the
5 step of administering a compound of claim 3.

20. A method for inhibiting the coagulation biological samples comprising the step of administering a compound of claim 4.

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60/135,849 24 May 1999 (24.05.1999) US
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- (74) Agent: LEE, Christine, S.; MORGAN, LEWIS & BOCKIUS L.L.P., 1800 M. Street, N.W., Washington, DC 20036-5869 (US).
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(54) Title: INHIBITORS OF FACTOR Xa

(57) Abstract: Compounds of the formula A - Y - D - E - G - J - Z - L in which D is a direct link, a substituted or unsubstituted phenyl or naphthyl group or a heterocyclic ring system; Z is a substituted or unsubstituted phenyl or naphthyl group or a heterocyclic ring system; and the other variables are as defined in the claims, their salts and compositions related thereto having activity against mammalian factor Xa are disclosed. The compounds are useful in vitro or in vivo for preventing or treating coagulation disorders.

INTERNATIONAL SEARCH REPORT

In International Application No
PCT/US 00/14205

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	A.M. ISMAIEL, ET AL.: "2-(1-Naphthyloxy)ethylamines with enhanced affinity for human 5-HT1Dbeta (h5-HT1B) serotonin receptors" JOURNAL OF MEDICINAL CHEMISTRY, vol. 40, no. 26, 19 December 1997 (1997-12-19), pages 4415-4419, XP002161081 American Chemical Society, Washington, DC, US ISSN: 0022-2623 compounds 3-6,8-12,14-17,19-22,24,25 ---	1
X	D.H.R. BARTON, ET AL.: "The catalytic effect of copper ions in the phenylation reaction of David and Thieffry" JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS, no. 1, January 1986 (1986-01), pages 65-66, XP002161082 Royal Society of Chemistry, Letchworth, GB ISSN: 0022-4936 compound 8 ---	1
X	L.W. DEADY, ET AL.: "A new synthesis of N-arylazetidines" TETRAHEDRON LETTERS, no. 14, 1968, pages 1773-1776, XP002161083 Elsevier Science Publishers, Amsterdam, NL ISSN: 0040-4039 compounds I; table I ---	1
X	G.F. GRILLOT, ET AL.: "Condesation of thiophenols and formaldehyde with some aromatic amines" JOURNAL OF ORGANIC CHEMISTRY, vol. 24, no. 8, 31 August 1959 (1959-08-31), pages 1035-1038, XP002161084 American Chemical Society, Washington, DC, US ISSN: 0022-3263 compounds I-VI,IX-XI,XIII,XIV,XVII,XVIII, XXIV; tables I,II --- -/--	1

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/14205

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	E. BÄDER, ET AL.: "Neue Methoden zur Darstellung von Sufonaminen (IV. Mitteil.: Polymerisationen und Polymerisationskatalysatoren)" CHEMISCHE BERICHTE, vol. 88, no. 1, 1955, pages 41-49, XP002161085 Verlag Chemie, Weinheim, DE ISSN: 0009-2940 table 1, entries 5,6,15-17 ----	1
X	S.T. MCDOWELL, ET AL.: "Elimination-addition. Part XI. Electronic effects upon the reactivity of aryl vinyl sulphones towards amines" JOURNAL OF THE CHEMICAL SOCIETY, SECTION B: PHYSICAL ORGANIC CHEMISTRY., no. 5, May 1967 (1967-05), pages 348-350, XP002161086 Royal Society of Chemistry, Letchworth, GB table 4 ----	1
X	A.W.M. LEE, ET AL.: "A facile total synthesis of isoquinoline alkaloids" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, no. 3, 1992, pages 309-310, XP002161087 Royal Society of Chemistry, Letchworth, GB ISSN: 0300-922X compound 2 ----	1
X	US 3 235 597 A (J. MILLS, ET AL.) 15 February 1966 (1966-02-15) example 1 ----	1
X	DE 10 62 253 B (FARBWEKE HOECHST) 30 July 1959 (1959-07-30) example 1 ----	1
X	J. L. BELLETIRE, ET AL.: "A useful approach to primary amines" SYNTHETIC COMMUNICATIONS, vol. 18, no. 1, 1988, pages 29-36, XP000982518 Marcel Dekker, Basel, CH ISSN: 0039-7911 the whole document ----	1
X	US 3 895 010 A (T.C. KLINGLER, ET AL.) 15 July 1975 (1975-07-15) the whole document -----	1

INTERNATIONAL SEARCH REPORT

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PCT/US 00/14205

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07C311/46 C07D213/74 A61K31/18 A61K31/277 A61K31/501 A61P7/02		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07C C07D A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) BEILSTEIN Data, WPI Data, EPO-Internal, PAJ, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 57934 A (DU PONT MERCK PHARMACEUTICAL) 23 December 1998 (1998-12-23) page 2 -page 8; examples; table 1 ---	1-20
A	WO 98 28282 A (DU PONT MERCK PHARMACEUTICAL) 2 July 1998 (1998-07-02) page 3 -page 9; examples; table 1 ---	1-20
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *Z* document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
26 February 2001		12/03/2001
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer English, R

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-3 (in part)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which part(s) of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

For these reasons it appears impossible to execute a meaningful search and /or to issue a complete search report over the whole breadth of the claim(s). The search and the report for those claims can only be considered complete for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds as indicated in the relevant examples (2,3,5-10) and claim 4.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.